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THE CONTROLLED CLINICAL TRIAL: THEORY AND PRACTICE*

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The doctor of today is under constant bombardment with claims as to the efficacy of drugs, old and new. It is difficult, if not impossible, to read a journal, attend a medical meeting, or open the morning mail without encountering a new report on the success or failure of some medication. The clinician who would avoid nihilistic rejection or trusting acceptance of all such claims, or capricious decisions as to their merits, is well advised to adopt a yardstick, a set of criteria, that will improve his chances of making sound evaluations. The investigator is equally well advised to do so. The present review will present one such set of guiding principles. In so doing it will pursue two main lines of emphasis. On the one hand, fundamental principles will be accented, not only to provide a framework for subsequent discussion, but to distinguish clearly between the important primary considerations and less essential embellishments and refinements of technique. On the other hand, these same principles will

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be scrutinized in detail and the complexities in their application in actual experiments described. This second line of emphasis is needed to avoid painting a picture of deceptive simplicity and to support the thesis that a doctrinaire insistence on literal and complete adherence to the principles *under all circumstances* can be achieved only by a cavalier dismissal of useful data or by the practice of self-delusion.

It is possible to summarize the fundamentals of the clinical trial[1-4] in the form of five principles. These are: (1) the cooperation of individuals with appropriate skills at all temporal levels of planning and execution; (2) randomization; (3) the "double blind" control; (4) statistical treatment of data; and (5) cautious generalization. Let us consider each principle separately.

A. THE JOINT NATURE OF THE CLINICAL TRIAL

Ideally, the clinical trial represents a fusion of talents, with different individuals contributing to the efficiency and quality of the experiment. This is merely the old principle of employing specialists when needed. Abuse of this principle is inadvisable at most times, but is especially foolhardy when an extensive, expensive, time-consuming project is planned. Although the make-up of such a team should obviously be appropriate to the experiment, a typical group might include a clinician, a pharmacologist, and a statistician (or multiples thereof). There are certain functions performed by the entire group, such as formulating a precise statement of the purpose of the clinical trial. Let us examine some of the particular functions of each member, however. It is currently fashionable in some circles to consider the clinician member of the team as some sort of minor excrescence, "a fifth cousin about to be removed." Such an attitude is arrant nonsense. The clinician is still in most such investigations the prime mover. It is generally he who is aware of the diseases requiring better therapy, of the symptoms inadequately treated. The clinician is also responsible usually for delineating the criteria for success or failure, and for devising methods for the gathering of pertinent data. It is the clinician who provides the all-important background for the clinical trial—knowledge, accumulated over the years, concerning the process under study. An example of the usefulness of this function may help to clarify the point. If one considers the field of antihypertensive drugs, it is apparent how helpful the body of knowledge on hypertension can be in setting up a clinical trial. How much more difficult the task would be, for example, did we not know that elevated blood pressure is a nonspecific manifestation of many disease processes; that even within the field of "essential" hypertension the prognosis varies from decades of unimpaired well-being to the brief downhill course of "malignant" hypertension; that the crucial body areas in this disease are the heart, the brain, and the kidneys. All this information enables the members of the team to focus on the appropriate goals of therapy, and points up the importance of such factors as patient selection and duration of study.

In addition, the clinician is at times in the enviable position of being able to make a real contribution to therapeutics without much outside assistance. I have in mind such disease processes as tuberculous meningitis, or acute staphy-

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lococcal septicemia, or acute leukemia, where past experience indicates a uniformly poor prognosis in the untreated case. If, then, a physician uses Drug A on a patient known to have such a disease and the patient is quickly and completely restored to permanent good health, the event is one of major importance. To criticize such a felicitous physician, who calls the case to the attention of his colleagues, because of a lack of placebo controls, or for not having a large series of similar cases, represents a naive display of pharmacologic Philistinism.*

The clinician should also bear the primary responsibility for reminding his associates of the ethical considerations involved in a proposed clinical trial. Let us suppose, for example, that two antibiotics are available, and that the laboratory evidence is conflicting as to whether the two drugs, when used together, are synergistic or antagonistic. In the case of an infectious disease for which there is no effective therapy, it is easy to justify a trial of the combination; the patients have nothing to lose and everything to gain. If no such conditions obtain, there may still be a disease process for which therapy is available but by no means optimal. Pneumococcal meningitis might be considered such a disease; subacute bacterial endocarditis another. Here one may be willing to entertain the risk of some loss of potency in a combination of drugs on the chance that a substantial synergism between the drugs might be demonstrated, with lifesaving effect for some patients. Let us take, however, a disease which is 100 per cent (or essentially 100 per cent) curable with presently available antibiotics. The trial of a new antibiotic on such patients, desirable as it may be from a variety of standpoints (e.g., a search for a cheaper or less toxic drug), must take into account the fact that the patients to be so treated are not likely to appreciate the importance of the data contributed by their own misfortunes to the welfare of unborn generations. Such patients have a good deal to lose by participation in such studies and very little to gain. If it is decided that the points at issue are of such importance that the trial has to be performed, adequate safeguards must be written into the clinical trial so that any patient who seems to be doing poorly on a particular regimen be switched without delay to standard forms of therapy. Such provisions have a good deal of nuisance value for investigators, and have at times ruined whole experiments, but only individuals devoid of empathy can argue that they are never necessary.

The contributions of the other members of the team should not be minimized. The pharmacologist can be most helpful in deciding whether the available data on the pharmacologic action or the toxicity of a compound in animals are such as to warrant its trial in human beings. He can also utilize his specialized talents to analyze what is known about the absorption, distribution, excretion, and fate of the drug, so that rational dosage schedules can be set up. If data on human beings are lacking, he can be invaluable in planning the cautious preliminary work that is so essential.

The statistician's aid is frequently indispensable. It is he who is most attuned to the need for safeguards against bias, for devising an experiment which is

*This is not to deny, however, that happy is the physician who can confirm his own work and twice happy is he who is confirmed by others.

free from systematic errors of allocation or assessment. He can comment critically on how pertinent the intended measurements are to the objective of the trial. An expert statistician can frequently increase the efficiency of a trial, so that the same amount of information can be elicited from a smaller number of patients or procedures. In evaluating data at the end of the experiment he can ensure that the appropriate analytic techniques be applied. Failure to utilize the aid of such specialists can be disastrous, as evidenced by a fiasco of some years ago. An ambitious polio vaccination program was responsible for the vaccination of some 450 children, while 680 in the same community remained unvaccinated as controls. An epidemic visited the area that year, but there was not a single recognized case of polio in either group. This was entirely consistent with the records of previous years, which indicated that only two cases could be expected in such a total number of children. A few simple calculations done (alas!) in retrospect revealed that meaningful data could have been obtained only by having 7,500 to 25,000 children in each of the groups.

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Having stressed the *cooperative* nature of the trial, one should also emphasize the phrase "at all temporal levels of planning and execution." Too often, for example, the statistician is called in at the end of a trial, in the hope that the chanting of a few mathematical formulas or Greek symbols over the corpse of an ill-planned experiment will restore the breath of life to the unfortunate victim. One eminent statistician has advised his fellows to eschew any part of a clinical trial in which they have not been active participants from its very inception. Such a remark may be a little extreme, but its point is well taken. In addition to participation at beginning and end, the members of the team should consult with each other during the progress of the trial. It is often difficult or impossible to foresee all possible contingencies, and it may be wiser to scrap an experimental design part way along, if serious errors in planning or execution manifest themselves, than to continue doggedly to the bitter end and find that the therapeutic egg which the investigators were so tenderly hatching had been in reality a billiard ball all the while.

Having said all this, it is only fair to add that the ideal conditions described previously are not always achievable, even with the best of intentions. "Full use of a biostatistician," for example, is easier said than done. Such individuals are relatively few in number and their time is limited even if funds are available to pay their salaries. The outlook is not as bleak as it may seem, however. It is perfectly feasible for a clinician with a working knowledge of statistics, and an appreciation of the principles to be described, to plan and execute a sound clinical trial, and to analyze the data satisfactorily. He may be somewhat inefficient in his methods but is not so likely to commit a basic error fatal to the entire enterprise.

B. THE PRINCIPLE OF RANDOMIZATION

It is difficult to conceive of a rule more important for the clinical investigator than that of avoiding bias in the allocation of cases to different treatment groups. If two drugs (or two procedures, or two surgical techniques) are to be compared,

it is obvious that the elimination of all variables other than the treatments in question is a prime goal. The conscious or unconscious distribution of one type of case (the "sickest" ones, for example) to a particular treatment group will introduce another variable into the design which will usually result in a completely useless experiment.* Such a procedure presents potentially different therapeutic challenges to the two treatments. Since it is difficult or impossible to gauge the degree of bias so introduced, or even its direction at times, the result of the study is usually to leave the experimenter no better off than when he began. The best way to avoid such bias is to assign cases by some technique which eliminates the possibility of prejudice. One may employ a randomized sequence (prepared in advance), or flip coins, or use even or odd last numbers on hospital admissions, or alternate cases. The important consideration is not which method is employed so much as the degree to which it succeeds in achieving an unbiased distribution. Thus alternate assignment of admissions to two groups is satisfactory only if the person in charge of admissions is unable to funnel cases selectively into one or another treatment group by the order of admitting them.

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It is unfortunate but true that the easiest way to allocate cases in more complicated situations is invariably the least desirable way. For example, if two hospitals are to compare the efficacy of two treatments it is much simpler, administratively, to give all the patients in Hospital Y one drug, and all the patients in Hospital Z the other drug. Such a plan may be disastrous, however, because of the excellent chance that the type of patients, the nursing, the medical staff will differ enough in the two institutions as to affect seriously the results *exclusive* of any possible difference between drugs. During the wartime evaluation of motion sickness preventives it was found that merely the amount of ballast carried by a troopship could affect the incidence of nausea and vomiting in the passengers. In addition, it was established that the section of the ship is an important determinant of the incidence of motion sickness. Thus, not only is it vital to compare medications on soldiers on the *same ship*, but it is imperative that all the treatments under study be allocated at random to the persons *within any given compartment* on the ship.

This principle of randomization is abused with such frequency that examples are easily found. One type of error is illustrated in a certain study of the effectiveness of anticoagulant therapy in the management of patients with cardiac infarction. Patients in this trial were assigned to the drug or nondrug groups on the basis of the day on which they were admitted to the hospital. Thus all patients admitted on odd days were allocated to the anticoagulant group, whereas those admitted on even days were given no anticoagulants. Since this plan is easily recognized by referring physicians, it becomes ridiculously simple to send in patients on a day when the type of therapy is such as the physician considers most appropriate for his patients. Thus, a physician who considers anticoagulants a dangerous and unnecessary measure could avoid sending his patients

*A classic example is the Lanarkshire milk experiment, where one-half the children got milk, but the teachers were permitted to assign the neediest ones to the milk group.[5]

in on odd days, so long as their clinical situation did not demand immediate hospitalization. Another physician who might be "sold" on anticoagulants could adopt just the opposite procedure, or at least attempt to get his "sickest patients" in on "anticoagulant days." The potentialities for bias are obvious. In this study 589 patients were treated and 442 patients were not. Thus, patients were probably not randomly selected since the excess of treated cases is greater than should be expected in a completely random selection of cases. One possibility is that physicians were in general eager to have their patients receive the "advantage" of anticoagulant treatment, and tried to refer patients in on treatment days. Since a critically ill patient would probably be hospitalized as rapidly as possible, it is also conceivable that there may have been a higher percentage of sicker patients in the untreated group.

Another type of error is to use as "controls" all patients who refuse a particular medication or procedure. Thus the postoperative history of a large series of hypertensive patients subjected to sympathectomy has been compared with the course of a large series of patients to whom the operation was tendered but who refused it. Even if one accepts the author's conclusion that the subsequent life history of the operated group was more favorable than that of the unoperated group, it is impossible to say whether the "improvement" is actually due to the surgery, or to the fact that the course of patients who refuse sympathectomy (for whatever reason) is basically less sanguine than that of their more pliable fellow sufferers.

Although the principle of randomization has thus far been discussed only in terms of cases allocated to different treatment groups, it is equally important for the order of administration of treatments to the same patient. For example, for each patient who, serving as his own control, takes Drug W for a period, then Drug Z for a similar period, it is essential for another patient to have this order of drugs reversed. The importance of the order of administration may be illustrated by a study of the effects of hypnotic drugs on psychomotor performance, on the morning after drug administration. One half of the subjects received the placebo on the first night of study, and pentobarbital on the second night, while the other half had this order reversed. The reason for this precaution was not only that the attitude of a subject might change on repetition of the experiment, or that he might become accustomed to the new environment, but that it is well known that most psychomotor tests show a significant "learning effect" with repetition. In order, then, not to underestimate or overestimate any difference between drug and placebo, no one treatment should be allowed to be always first or always second. In this situation, the "learning effect" was appreciated in advance. Regardless of whether the order of administration has been previously demonstrated (or can be reasonably expected) to be important in determining results, however, the wisest procedure is to assume that it will and to proceed accordingly.

A second example can be culled from the literature on coronary vasodilators. One group of investigators observed that outpatients suffering from angina pectoris usually improved during their first few weeks in the clinic regardless of

what they were given. Although these investigators did not pursue this observation to its logical conclusion (they always gave the placebo first), it is clear that randomization of order of treatments would be the preferred procedure.

The use of the principle of randomization eliminates the need for separate listing of another principle—that of concurrent comparison. This latter concept is designed to eliminate differences between groups arising from the fact that they were studied at different periods of time. It is very unwise, for example, to compare the results of treatment with veratrum in a group of hypertensives studied in 1954 with an untreated group studied in 1934. Even if no specific measures against hypertension were available now, it is possible that a group of patients treated today would do better in any event because of other advances in therapy since 1934. (Obviously a patient with hypertension is less likely to die of infections today than he was twenty years ago. Similarly, if he goes into shock for any reason today, he is in a much better position, because of the widespread availability of blood and blood substitutes, than he was in 1934.) If the error is compounded by utilizing the 1934 data of another clinic in a different part of the country or the world for comparison, the additional possibility of differences in diagnostic criteria or patient selection (already somewhat present in the first situation) is introduced to wreak further havoc with the validity of the investigator's comparisons.

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C. THE "DOUBLE BLIND" TEST

The third major principle is directed to the elimination of "errors of assessment." It is commonly referred to as the "double blind" or "double blindfold" test and consists of attempts to keep both patient and observer unaware of the nature of the medication being given. Thus, if one group of patients is to receive a potent drug and another group is to receive placebos, the patients and observers are kept in ignorance as to which group is which. If the same patient is to receive, on different occasions, a drug and a placebo, neither he nor the person responsible for evaluating the results of therapy is informed of which is the control period and which is the drug period. The bias which these precautions are primarily designed to eliminate is that attributable to "patient enthusiasm" or "investigator enthusiasm." Most patients with disease want to get better, and most investigators are anxious to come up with successful results. Both patient and investigator, therefore, may be tempted (on a conscious or unconscious level) to record improvement in symptoms under treatment. This enthusiasm must therefore be handled by allowing it to diffuse itself out as equally as possible over the active and inactive medications.

There are some situations where prejudice of this sort is very easy to introduce, and others where it is very difficult. For example, pain is known to be present or absent in a patient only if he tells us so. Pain is also composed in part of a psychologic ("emotional") reaction to certain neurophysiologic stimuli. In such a situation, subjective reaction is all-important, and it is easy to see how the results of medication can be affected by suggestion or wishful thinking. On the other hand, if the end point in a clinical trial is survival or

death, it is unlikely that there will be much understatement or overstatement on the part of the patient or observer.

The usual way of avoiding errors of assessment is to use placebos. Such pharmacologically inert substances (which some prefer to call "dummy" tablets or injections) are usually described as "indistinguishable" from the medication under study. By this is usually meant that the two medications look, smell, and taste "alike." These active and inactive medications are then designated by code letters or names and their true nature is known only to certain individuals not directly concerned with the accumulation of data. These codes are preferably changed at frequent intervals so that the results of previous trials cannot influence subsequent data.

So far, so good. Let us examine the placebo somewhat more critically, however, since it and "double blind" have reached the status of fetishes in our thinking and literature. The Automatic Aura of Respectability, Infallibility, and Scientific Savoir-faire which they possess for many can be easily shown to be undeserved in certain instances.

First of all, there is a mistaken notion that placebos merely control "suggestion" or "suggestibility." There is no question that this is partly their function, although it is not true that symptoms can be improved by a placebo only if they are of psychologic (nonpathologic) origin. But placebos control something else. They also are used to control naturally occurring, that is, spontaneous, changes in the course of disease. Many processes improve sans therapy of any sort. In a recent study of hypnotics in preoperative patients, it was found that 70 per cent of placebo-treated individuals fell asleep satisfactorily. This superficially implies a rather suggestible group. Quite the contrary seemed to be true, however, for the percentage of patients falling asleep successfully in a similar group *receiving no medication at all* (drug or placebo) was almost identical with that in the placebo group. The placebo rate in this instance was thus primarily a reflection of the ability of a group of such patients to fall asleep under certain specific conditions regardless of medication. Such a situation can be appreciated only if one contrives an experiment so that there are control periods (or groups) when nothing of any sort is given and which may be compared with a placebo-treated period (or group). Such a design involves more subjects, time, and effort, and may not be justified by the interests of the experimenter, but it behooves the latter to be cautious in his interpretations of "placebo effects" if he does not include an "untreated" group.

A second misconception about placebos is the belief that they always fool the patient or the observer. With a medication which produces no effects, subjective or objective, other than the one under study, this is possible. Many drugs, however, *do* produce side effects. A good-sized nitroglycerine tablet, for example, will hardly be confused with a lactose tablet by a reasonably alert person once he has had it under his tongue for a few minutes. Most subjects who have never previously received an injection of morphine can quickly tell 15 mg. of this drug from an injection of saline solution. They may not experience euphoria, but they will very likely be dizzy, or nauseated, or sleepy. (Indeed an experimental population which could not distinguish between the two would

be useless for many purposes.) Therefore, if such a subject can voluntarily affect some measurement being studied, it is a simple matter to bias the results regardless of "placebo controls." It should be stated, however, that there are all degrees of recognition of medications. Thus a novice to narcotics can distinguish morphine from saline solution, but a postaddict can also recognize that it *is* morphine, which complicates matters still further. The perfect placebo, therefore, would be one which would mimic exactly all qualities and effects of the drug under study *except* for the effect in question. Obviously, in many cases the achievement of the perfect placebo is an actual impossibility.

The placebo can also fail miserably in eliminating "negative" bias, that is, tendencies on the part of a patient or investigator to deny any effect of a drug, or to deny differences between drug and placebo. Thus, a patient receiving morphine and placebo alternately for pain can, by the simple expedient of calling every dose of medication effective (or ineffective), mask the differences between the most potent and least potent analgesics available. Similarly, let us suppose that a neurologist is convinced that the injection of the stellate ganglion with procaine is a ridiculous treatment for cerebrovascular accidents. Regardless of the fact that someone else sees to it that alternate cases are treated with saline solution and procaine, and that the neurologist is unaware which patient got which, if the neurologist in question is in charge of evaluating the therapeutic results, he can bias the data beautifully by merely writing "no significant improvement" in all cases. The net result will be no difference between drug and placebo. The safeguards against this latter kind of "negative bias" are first of all the predominant tendency, previously mentioned, toward "positive" bias, and second the fact that a failure to demonstrate differences between treatments can only be interpreted as "no difference was demonstrated" ("not proved"), rather than "no difference exists" ("not guilty").

A word should also be said about certain difficulties arising from the use of placebos because of either practical or ethical considerations. If one is trying to evaluate an analgesic drug, for example, the inclusion of placebos in the experimental design is difficult to rationalize from the patient's standpoint, because drugs of established potency are available which will do a reasonably good job of relieving symptoms. Fortunately, this fact can be utilized in the design in a way which will at least partly solve the problem of controls. One can use a standard drug (morphine, for example) and compare the new drug with it at several dose levels. The answer will thus be to the question, "How good is the drug in comparison with morphine?" rather than to the question, "How much better than a placebo is this new drug?" In such a study, every other dose can be of the standard medication so that even if the new drug is ineffective, the timing of doses can be such that a patient does not go very long without getting an effective medication. Such a procedure not only provides comfort for the patient, but also maintains rapport with the medical and nursing staffs responsible for the patients, who soon become aware of difficulties if multiple placebos are given. With a disease like tuberculosis, one of a variety of available drugs can be employed as similar "standards" to serve as yardsticks instead of placebos.

Such techniques are not perfect solutions because it is often extremely interesting and important to know whether a drug is any better than a placebo. In addition, the presence of considerable numbers of "placebo reactors" may result in an underestimation of the optimal dose for the population at large. Further, a number of reports now indicate that the separate handling of data from "placebo reactors" and "nonreactors" may bring out differences between drugs not obvious in the unselected data.[6,7] It has been suggested that a possible solution to the latter problem may lie in the focusing on patients with symptoms of severe degree, since there is evidence that the patients with more severe pain, for example, are less likely to get relief from a placebo than those with less severe pain, and it seems reasonable that severity of other symptoms may likewise be inversely related to placebo success rates.[8] (The extreme of this approach has already been discussed, and is exemplified by such diseases as tuberculous meningitis.) There are dangers in this approach, however. If one studies a new diuretic drug in patients with "intractable" congestive failure which is refractory to the usual therapeutic procedures, a successful outcome is most impressive. A negative result is less easily interpreted. One cannot say that the new drug is completely without effect, because such patients are by definition refractory to digitalis and mercurials, which would thus also qualify as "inactive drugs" in these same patients. Therefore, a negative result in such a difficult therapeutic situation should usually be followed up by studies in less severely ill patients. It is rare to come up with a superdrug, and it would be unfortunate to miss a compound of moderate potency.

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Finally, an example should be given of a trial that was conducted without the benefit of a "double blind" control of all aspects, but which nevertheless yielded useful data. The study by the Medical Research Council of Great Britain on the treatment of pulmonary tuberculosis with streptomycin was performed by allocating patients at random to two groups, one group of which received streptomycin, while the other group received only bed rest. This second group was not given placebos, and the physicians in charge of the two groups obviously knew which patients were receiving the drug and which were not. The major safeguard in this study was the reliance on objective criteria, such as fever, sedimentation rate, weight, x-ray changes, and survival rate. As already mentioned, the latter criterion seems hardly liable to biased recording. As an added precaution in studying the x-ray changes, however, the roentgenograms were interpreted by physicians who were unaware of the names and treatments of the patients. Since both the x-ray results and the mortality were strikingly different in the treated and untreated groups, there was little question that a new therapeutic agent was at hand. A purist might say that it is possible that the mere suggestion of potent therapy involved in being stuck four times a day for four months might have produced the beneficial results. To interpret a decrease in mortality from 27 to 7 per cent as a placebo effect in this situation seems a trifle captious, however.*

*Dr. Paul Meier suggests that unfortunately this is just the sort of remark often made to justify a poor experiment. He is, of course, entirely correct, which points up how difficult life can be.

D. STATISTICAL TREATMENT OF DATA

The fourth major principle refers to the analysis of data in a sophisticated fashion so that one can answer such important questions as "What are the chances that the observed differences between treatments may have been due to chance alone?" or "How reliable are my estimates of the potency of these drugs?" Let it be emphasized that a flagrant disregard of one or more of the principles previously described usually renders it unnecessary to apply *any* statistical techniques to the data. For example, if a series of patients is subjected to portacaval shunts, and the first fifty are performed under ether and the next fifty under cyclopropane, it is unsophisticated to make a detailed analysis of the results in the two groups with the notion of comparing the relative safety of the two anesthetics. There are obviously other variables involved with the passage of time (increasing experience and skill of the surgical team, differences in patient selection, and so forth) that would render it impossible to state that any significant differences between groups were actually due to the anesthetic agents. In such a situation it is sounder merely to tabulate the incidence of deaths, complications, therapeutic results, and so forth, and present the results as "our experience during the first two years" versus "our experience during the last two years."

For those of us who are not professional statisticians, it is always most reassuring to have expert help with the final analysis of data. Frequently, one reads papers in which the use of inappropriate statistical techniques has either failed to show significance where such exists or has "demonstrated" significance where none actually exists.

As an example of the latter type of error, one can cite the failure of investigators to make an over-all chi square test or analysis of variance on the total data to find whether individual comparisons of pairs of treatments are warranted. Even if one compares treatments *of equal effectiveness*, there will be a spread of "cure rates" which will vary over a range the size of which is partly determined by the number of treatments. It has been calculated that if one compares the highest and lowest "cure rates" in such an experiment, "significant" differences "at the 5 per cent level" will be "demonstrated" 13 per cent of the time if 3 treatments are used, 40 per cent if 6, and 90 per cent if 20 treatments are run! Obviously, then, to study 5 drugs and 2 placebos and then say that the "best" drug differs from the placebo "at the 5 per cent level" really means little unless one runs an over-all chi square first.*

An example of the inappropriate evaluation of data where just the opposite effect is obtained has been given by Mosteller.[7] If 100 patients each receive 2 drugs at different times, and one analyzes the following incidence of nausea by an ordinary 2 by 2 contingency table:

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*As in all areas of human endeavor, there is disagreement among statisticians as to the preferred method of attacking problems. The performance of an "over-all" test followed by t tests is a time-honored and popular procedure, but recent workers (Scheffé, Tukey, and so forth) have proposed substitute tests which seem more reasonable or sophisticated to segments of the profession.

	NAUSEA	NOT NAUSEA	TOTAL
Drug A	18	82	100
Drug B	10	90	100
Total	28	172	200

the results are not statistically significant. Such an analysis, however, is not only predicated on independent samples, and therefore incorrect in these matched data, but is also inefficient since it does not make use of the fact that each person who is nauseated after one drug is more likely to be nauseated after the second drug. Actually, we are not interested in people who are either nauseated with both, or with neither. The only information on differences between the drugs is derived from those individuals who have nausea with one but not with the other. Analyzing the data from this standpoint, we find that 9 of the patients had nausea with both drugs, 81 with neither, 9 after Drug A but not Drug B, and 1 after Drug B but not Drug A. A new table can thus be set up, as follows:

		DRUG A		
		NAUSEA	NOT NAUSEA	TOTAL
DRUG B	NAUSEA	9	1	10
	NOT NAUSEA	9	81	90
	TOTAL	18	82	100

Analysis of these figures by a simple formula gives highly significant differences.

A word should be said about two diametrically opposed tendencies which I think are equally mistaken. Both are the result of an overzealous worship of the magic "$p = 0.05$." This latter figure means that the differences would have been observed only 5 times out of 100 due to chance alone, and that there are 95 chances in 100 that the observed differences are real ones. This common standard has been chosen because it seems like a reasonable compromise between the error of saying something is significantly different when it is not and of saying that something is not significantly different when it is. Let us examine some ways in which this value can be abused. Let us say that as a result of hundreds of observations, one drug is found to be a few per cent more effective than a placebo in relieving cough. The p value for this difference may be < 0.05, but what real meaning does this have? How important is it to know that a drug is "microscopically" better than no drug at all? On the other hand, suppose that one makes a small study on two antitussives and both turn out to be significantly better than a placebo, but in comparing the two drugs against each other, Drug A just misses being significantly better than Drug B (p of 0.06, for example). To dismiss this difference as completely meaningless seems rash. If possible, and if it were important enough, the experiment should be repeated

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with larger numbers. If the experiment cannot be repeated, and there are no other data available for coming to a conclusion on the relative merits of the two medications, one would be justified in using the *apparently* better of the two.

Statistical techniques are essential in problems of "estimation." If an experiment is run on a diuretic drug, it is one thing to know that it can cause patients to lose fluid, but it is equally or more important to be able to state *how much* fluid can be expected to be lost by, let us say, 95 per cent of patients. For such an estimate we are concerned with putting limits ("confidence limits," so-called) on our estimate of the fluid loss in the population studied. Obviously, a drug which will cause almost all patients to lose 2.5 to 3.5 pounds differs from one which may produce responses varying from 0 to 20 pounds. Predictability of response is usually of considerable importance in the evaluation and use of a drug, and statistical analysis provides a measure of predictability, whether one is concerned with the magnitude of effect of a given drug, or the magnitude of the difference between two drugs.*

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E. CAUTIOUS GENERALIZATION

The final principle to be discussed is the principle of cautious generalization. The problem of transposition of data and conclusions from one experimental setup to others is a fundamental one, of course, for many areas of scientific endeavor. The action of morphine in patients with increased intracranial pressure or severe pulmonary disease may be at least quantitatively different from its effects in normal individuals. The action of digitalis in patients with congestive heart failure is hardly the same as its effects in a normal individual. The pain of childbirth is different from the pain of chronic headache. Many such examples could be given to illustrate this point. Reports of the efficacy or inefficacy of a medication should always be qualified with phrases such as "under the conditions of the experiment," "with these dosages," "in these patients," and so forth. There are many instances of disagreement in the medical literature on results obtained with various drugs. Some of these differences are easily explained by experimental technique, dose, duration of study, and so forth. Many are not, however, and it would seem appropriate to be generous in such instances, assume the honesty of the investigators, and look elsewhere for explanations.

One possible source of error which has been emphasized recently[9] is the frequent use of volunteers as subjects for studies, the results of which are ultimately applied to more general situations. It is quite apparent that volunteers may differ quite markedly from the nonvolunteers in their own group, let alone from individuals in other groups. This is not to say that such studies are useless—indeed, they are the only studies possible in many circumstances. One must, however, be careful to use such data for what they are worth and rely on subsequent confirmation in other situations before generalizing broadly.

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*For example, an experiment may show two drugs to differ in mean effectiveness by 20 per cent, but it is most helpful to state that from the data one is almost certain that the "true" difference is not less than 10 or more than 30 per cent.

One other source of error is the use of fractions of an experimental population chosen because of certain characteristics which make an experimental study easier for the investigator than if a random sample were chosen. An example is the choice of 52 patients of a group of 3,000 patients with angina pectoris for a study on vasodilator drugs. This small sample was chosen because its members responded consistently (from an electrocardiographic standpoint) to exercise and because they showed favorable response to nitroglycerine. Making a study on such patients is perfectly permissible, but it may not tell much about the average patient with angina pectoris, who obviously did not qualify for the study. In addition, the method of selection made it inevitable that no drug studied would outperform nitroglycerine, since the best that any drug could do was to equal its performance.

Obviously, the most satisfactory situation with regard to a drug is to have its performance tested carefully by a variety of independent observers in different clinics with different types of patients under different conditions. If such studies are in general agreement as to the drug's efficacy, there is little room for doubt. On the other hand, a single negative or positive study, no matter how carefully performed, must always leave some question unanswered.

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FINAL COMMENTS

These principles, then, seem the crucial ones for conducting clinical trials or evaluating their results. It is hoped that the picture drawn seems neither too confusing nor overly simple. The principles are simple but their application is frequently not. As in so many fields, a middle course is actually the wisest one. In the field of the clinical trial, the Golden Mean is not "a virtue flanked by two vices" but the only rational approach. I should like to discuss briefly some additional personal sources of humility in this field.

First, there is the fact that frequently a careful clinical trial merely substantiates what has been previously determined by uncontrolled experiments. This is not always so, but many instances can be cited. For example, the carefully done analgesic studies of the group at the Harvard Medical School Anesthesia Laboratory have for the most part defined equianalgesic doses of drugs which are in agreement with those already determined by clinicians at the bedside. Such valid observations obtained by clinicians in an uncontrolled way are particularly likely to be made if a drug is exceptionally potent or toxic, if the disease process being studied is one not likely to improve spontaneously, or if a potent drug is already available for comparison. Although once again one can cite exceptions, it thus behooves investigators who come up with completely negative studies on a time-honored drug to be exceptionally careful in dismissing the medication as inactive. Too frequently the next investigator devises a satisfactory testing situation and corroborates past generations of maligned clinicians.

Finally, for those who like to think that satisfactory clinical trials are new and a part of the pharmacology of the last decade or so, I should like to quote the following, abstracted from an article by Gaddum.[3]

" . . . I took twelve patients . . . (with) scurvy. . . . Their cases were as similar as I could have them. . . . They lay together in one place and had one diet common to all. Two of these were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir of vitriol three times a day upon an empty stomach. Two others took two spoonfuls of vinegar three times a day. . . . Two of the worst patients were put upon a course of sea-water. Of this they drank half a pint every day. Two others had each two oranges and one lemon given them every day. The two remaining patients took an electuary recommended by a hospital surgeon made of garlic, mustard, balsam of Peru and myrrh. The consequence was that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them being at the end of six days fit for duty. The other was the best recovered of any in his condition and was appointed nurse to the rest of the sick."

This experiment was started by James Lind on May 20, 1747.

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DIABETES MELLITUS MORTALITY IN THE CONTINENTAL UNITED STATES—1950

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IN 1950 diabetes mellitus caused the death of 24,419 persons (16.2 per 100,000 population), ranking tenth as a cause of death in the continental United States. In 1951 there were 25,047 deaths from diabetes (ranking ninth), in 1952 there were 25,474 (ranking eighth), and according to provisional figures there were an estimated 25,390 deaths in 1953 (ranking eighth).

In addition to these persons dying *from* diabetes, a large number of persons *with* diabetes die from vascular degeneration and are classified in one or another of the categories of the cardiovascular-renal conditions. Opinion differs regarding the proportion of such deaths basically caused by diabetes. This paper will confine itself to reported deaths *from* diabetes mellitus, coded according to the Sixth Revision of the International List of Causes of Death (code 260) in 1950, and to trends in reported mortality from diabetes.

AGE, SEX, AND RACE

Diabetes is not of equal significance as a cause of death in all segments of the population. In 1950 the diabetes death rate for white females was 20.0 per 100,000, followed by nonwhite females (18.7) and white males (12.8); the rate for nonwhite males (10.0) was only one-half the rate for white females.

Diabetes causes more deaths in older persons, with the rates increasing with age. In the age group 65 to 74, it ranked fifth as a cause of death, fourth for white females, sixth for nonwhite females, eighth for white males, and twelfth for nonwhite males.

For white persons there is no essential difference between the sexes in death rates from diabetes in the younger age groups; after age 45 the rates are higher for females than for males in each group. In nonwhite persons the rates appear to be higher for females at all ages.

Diabetes presents the interesting but not unusual phenomenon of higher mortality rates for nonwhite than white population groups in the early years of

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life, but lower nonwhite than white rates in the later years of life. This change in excess mortality from nonwhite to white also occurs in cancer, the cardiovascular diseases, the anemias, and ulcers of the stomach and duodenum. It is, however, most pronounced for diabetes, and occurs at about age 65 in both sexes.

TABLE I. DIABETES MELLITUS—DEATH RATE PER 100,000 AND RANK AS CAUSE OF DEATH BY AGE, RACE, AND SEX, CONTINENTAL UNITED STATES, 1950

AGE GROUP	TOTAL		WHITE MALE		WHITE FEMALE		NONWHITE MALE		NONWHITE FEMALE	
	RATE	RANK	RATE	RANK	RATE	RANK	RATE	RANK	RATE	RANK
All ages*	16.2	10	12.8	12	20.0	8	10.0	15	18.7	9
5–14	0.6	14	0.5	15	0.6	12	0.3	19	1.1	11
15–24	1.1	14	0.8	16	1.2	13	1.7	12	2.6	11
25–44	3.1	12	2.9	12	2.4	12	5.5	14	9.0	12
45–64	25.4	7	18.5	11	29.3	4	24.5	11	59.2	7
65–74	100.3	5	77.0	8	125.2	4	60.9	12	98.0	6
75–84	166.7	8	145.7	9	192.7	7	88.2	11	108.4	9
85 and over	150.3	10	147.6	10	159.9	9	58.9	11	122.5	9

Source: National Office of Vital Statistics. Rank based on the 64 cause list. Ranks for age group over 64 computed in Program Analysis Section, Chronic Disease Program, Public Health Service.
*Includes children under 5 years of age.

Fig. 1, in which nonwhite and white rates are plotted, shows the increasing relative death rates from diabetes in white persons in the older age brackets. It is this higher death rate from diabetes among the older white persons that accounts for the higher crude rate among white persons (16.4 vs. 14.4); the nonwhite rate adjusted for age is higher than the white rate (18.7 vs. 16.4). It also accounts for the higher median ages at death from diabetes for white persons (nonwhite female 58, nonwhite male 60, white male 68, and white female 69).

MARITAL STATUS

The over-all death rate from diabetes mellitus is higher for married (including widowed and divorced) females than for single females or either single or married males. (See Table II and Fig. 2.) From about age 50 on, the age-specific rates for married women are considerably higher than for married men.

Deaths from diabetes in younger persons are comparatively few, but in the younger age groups the rates for single persons are higher than for married persons. Deferment of marriage and hesitation to marry by young diabetic persons have been suggested as possible reasons for this phenomenon.

The difference in mortality rates between married women and other groups in 1950 showed up at about age 50 and increased until about age 80. It has been suggested that the experience of pregnancy with its metabolic changes may, in a susceptible individual, be a precipitating factor in the development of frank diabetes in later years.

The data by marital status for 1950 indicate that some other factors may be associated with the differences indicated. As shown in Fig. 2, the rates for

all married men were higher from about age 65 on than those for single men or women. Inspection of Table II shows in general higher diabetes death rates for males among the widowed and divorced than among those who were single or still married at the time of death.

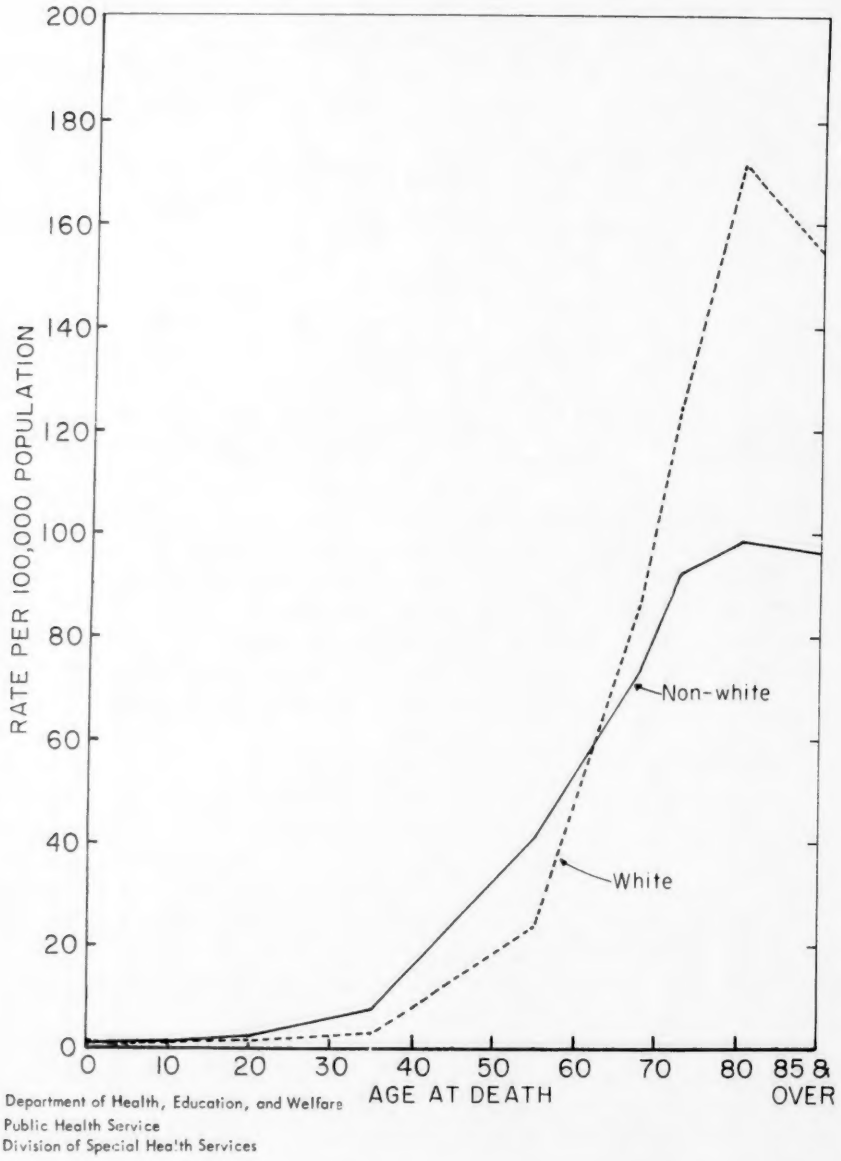

Fig. 1.—Death rates from diabetes for white and nonwhite persons by age: continental United States, 1950.

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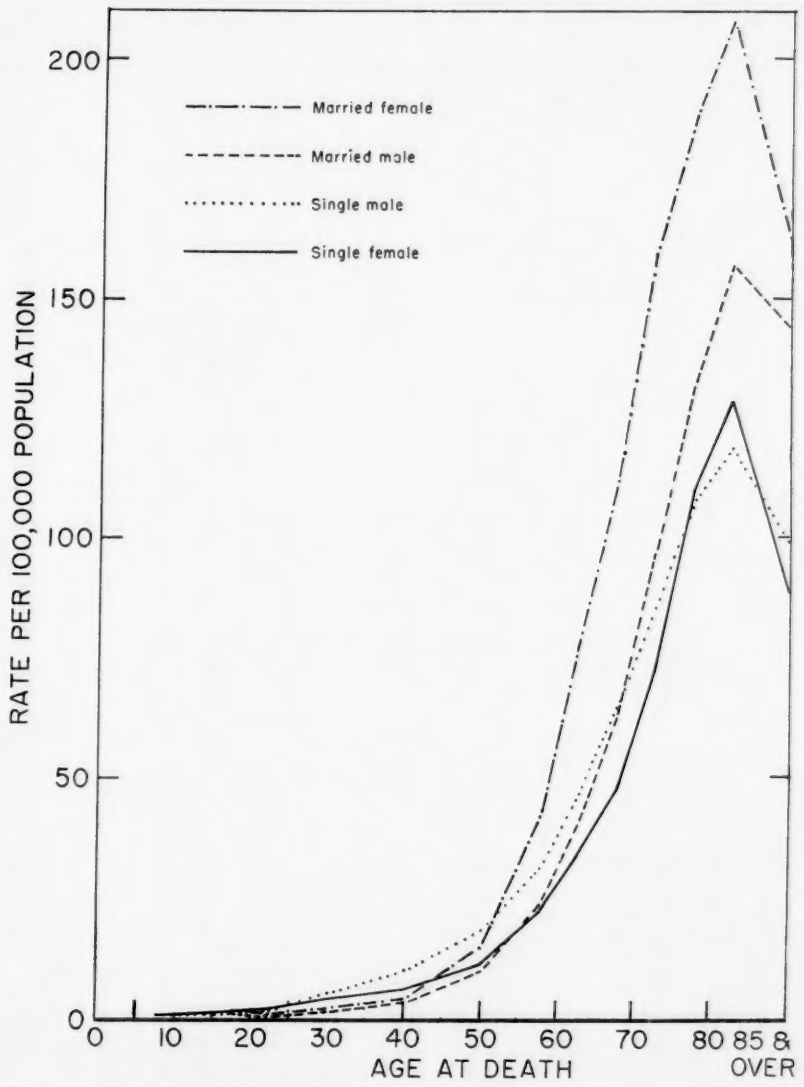
URBAN OR RURAL RESIDENCE

Deaths from diabetes are reported with relatively more frequency by incorporated urban than by "rural" areas. The rate in 1950 for all incorporated places of 2,500 or more inhabitants is 19.0 compared to 12.4 for "rural" areas,



Department of Health, Education, and Welfare
Public Health Service
Division of Special Health Services

Fig. 2.—Death rates from diabetes mellitus by age group, sex, and marital status: continental United States, 1949-1951 (average).

TABLE II. DEATH RATES PER 100,000 FOR DIABETES MELLITUS BY AGE, SEX, AND MARITAL STATUS, CONTINENTAL UNITED STATES, 1950

AGE GROUP	MALE					FEMALE				
	TOTAL	SINGLE	MARRIED	WIDOWED	DIVORCED	TOTAL	SINGLE	MARRIED	WIDOWED	DIVORCED
Total	12.6	3.3	16.3	84.7	27.2	20.2	3.3	18.8	104.7	18.3
Under 20 years	1.4	1.4	0.6	5.0	0.0	2.2	2.1	1.6	5.7	4.0
20–24 years	1.2	1.5	0.7	0.0	0.7	1.4	1.8	1.2	1.3	2.1
25–34 years	2.2	5.1	1.4	4.6	6.1	2.1	4.2	1.7	4.2	3.3
35–44 years	4.0	10.2	3.1	7.7	12.2	4.0	5.8	3.5	10.1	4.9
45–54 years	10.9	18.5	9.4	23.3	20.1	14.7	11.3	13.8	24.1	12.6
55–59 years	24.6	31.5	23.0	33.2	33.1	40.6	22.3	39.8	50.9	34.8
60–64 years	41.2	47.2	38.8	53.0	52.2	74.5	34.0	75.9	83.3	66.0
65–69 years	63.4	65.1	59.9	76.6	82.7	107.3	47.9	109.8	117.0	90.3
70–74 years	96.0	86.1	93.5	105.2	120.7	152.0	72.6	160.3	159.5	168.1
75 years and over	138.7	110.4	135.3	147.6	185.2	182.7	112.3	190.2	189.4	264.7

Sources: Deaths by marital status from unpublished data from the National Office of Vital Statistics. Average of 1949-1951 data taken as representing 1950.

Population from 1950 Census Population Reports PC-1, Table 102 and PB-1, Table 38. Excludes armed forces overseas.

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including urbanized but unincorporated suburbs. To what extent these differences are the result of a higher prevalence of diabetes in urban areas, different case fatality rates, or differences in reporting systems, we do not know.

We have not found any relationship between size of city and the diabetes death rate. In fact, cities of 2,500 to 10,000 have as high a rate as the cities of 1 million and over. Table III presents the data for cities of different sizes. Except for cities of 250,000 to 500,000 the rates are uniformly high. An explanation of the rate of 15.9 for those cities might be that a higher proportion of them are situated outside the East and North Central portions of the United States than is true of the larger or smaller cities.

TABLE III. DEATH RATE PER 100,000 POPULATION IN CITIES OF 2,500 OR MORE POPULATION BY SIZE OF CITY, CONTINENTAL UNITED STATES, 1950

SIZE OF CITY	POPULATION 1950	DEATHS FROM DIABETES	RATE PER 100,000 POPULATION
1,000,000 or more	17,404,450	3,418	19.6
500,000–999,999	9,186,945	1,782	19.4
250,000–499,999	8,241,560	1,309	15.9
100,000–249,999	9,478,662	1,761	18.6
50,000– 99,999	8,930,823	1,693	19.0
25,000– 49,999	8,710,867	1,706	19.6
10,000– 24,999	11,515,155	2,205	19.1
2,500– 9,999	13,082,479	2,584	19.8
Urban—Total*	86,550,941	16,458	19.0
Rural	64,146,420	7,961	12.4
Total U. S.	150,697,361	24,419	16.2

*Urban includes incorporated places of 2,500 or more (Census Bureau old definition).

GEOGRAPHIC AREA

Although a large proportion of the persons with diabetes are classified at death as dying from other causes, and this proportion varies from area to area, still the distribution of reported diabetes deaths may be indicative of the distribution of diabetes prevalence.

There is considerable variation from state to state and from region to region in mortality rates from diabetes. In general, the Northeast and North Central States have the highest rates and the South and West the lowest (Fig. 3).

Many factors undoubtedly influence the variation in the diabetes death rate between states and between regions. The differences may result partly from real variations in the death rate from diabetes due either to varying case fatality rates or to varying prevalence rates. They are, in part, reflections of differences in age,* sex, and race distributions of the populations in the various

*Adjusting for age changes somewhat the rank order of states, but affects only slightly the states in each interquartile range. The only major shift was South Carolina from the second lowest group (13.4) to the highest group (19.1).

states, the degree of urbanization of areas, differences in social, economic, and cultural patterns of the population groups, and differences in the availability of medical facilities and in patterns of reporting causes of death.

One of the factors that has been considered for the United States as a whole is the higher mortality from diabetes recorded among residents of urban areas. As shown in Fig. 4, rates of diabetes mortality for cities of 100,000 or more population are higher in the Northeast than in other parts of the country. Of the twenty-one cities with the highest diabetes death rates—ranging from 23.4 to 36.2—only one is south of Ohio or Delaware and none is west of Indiana. Most of the twenty-one cities ranking in the second highest quintile range of diabetes death rates (from 20.1 to 23.3) are also in the Northeastern region, and the only city west of the Mississippi is St. Louis. The twenty-one cities with the lowest death rates, 4.8 to 11.8, are all in the West or in the South.

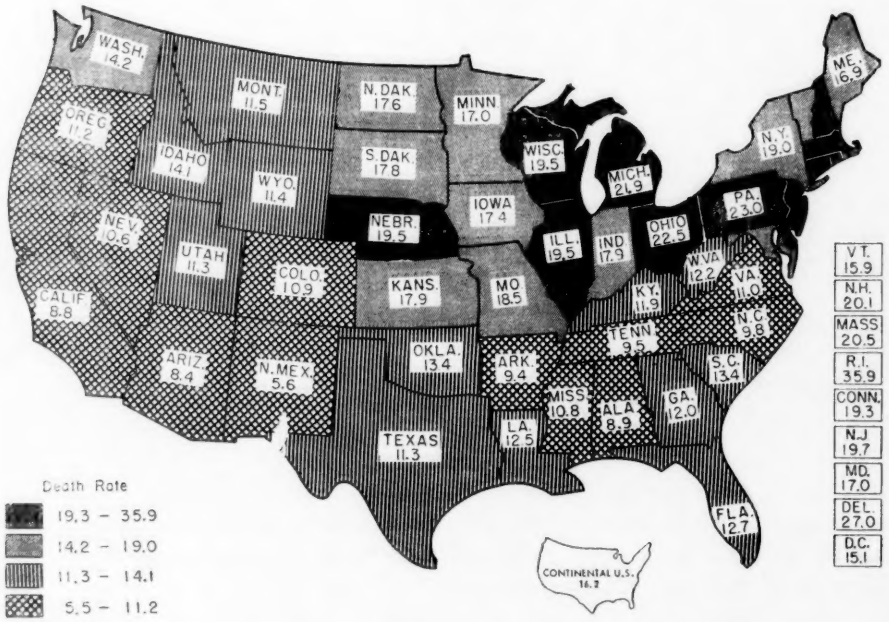


Fig. 3.—Diabetes death rates: continental United States, 1950.

PROPORTIONATE MORTALITY FROM DIABETES IN 1950 BY STATE

Diabetes, even under the classification provided by the Sixth Revision of the International List, remains a leading cause of death from disease. However, the percentage of all deaths attributed to diabetes as the primary cause (proportionate mortality) was only 1.7 for the continental United States in 1950.

Proportionate mortality from diabetes varied among the states from a low of 0.7 in New Mexico to a high of 3.4 per cent in Rhode Island. These two states had the lowest and highest diabetes death rates, whether crude or age-adjusted. In general, proportionate mortality was highest where death rates from diabetes were high. When the states were divided by quartiles according to crude death rates and again according to proportionate mortality, thirty-six states fell into the same interquartile range on both counts. The other twelve states and the District of Columbia were in adjoining interquartile ranges when ranked according to proportionate mortality and crude death rates.

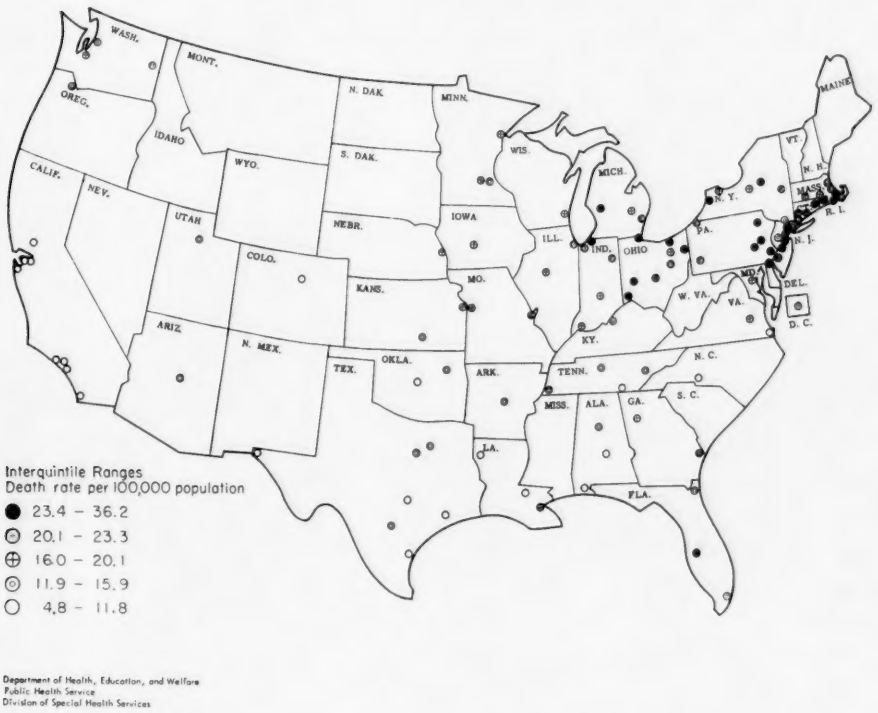


Fig. 4.—Diabetes death rates: cities with population over 100,000, United States, 1950.

TREND OF DIABETES MORTALITY

The trend of crude death rates from diabetes has been upward since 1900 (Fig. 5), with a tendency to level off in recent years. Because the mortality rate for diabetes increases with age, a gradual increase would be expected in an aging population. The crude rates were lower in the earlier years and higher since 1940 than rates adjusted to the age distribution of 1940. Up to 1940 there was an increase, which age adjusting does not remove.

Revisions in the International Lists of Causes of Death did not directly affect the position of diabetes as a cause of death until 1949, when the Sixth

Revision became effective. The former practice in this country was arbitrarily to assign the primary cause of death when diabetes and certain other conditions were mentioned on a death certificate, according to a system of priorities for joint causes of death. The only causes previously given priority over diabetes were tuberculosis, cancer, puerperal and acute surgical conditions, and violence. Mose people *with* diabetes, however, do not die *from* diabetes, but from other causes, particularly arteriosclerotic complications. When a 10 per cent sample of death certificates for 1949 and 1950 was coded according to both the Fifth and Sixth Revisions, the number of deaths coded as caused by diabetes was only 57 per cent as high under the Sixth as under the Fifth Revision.

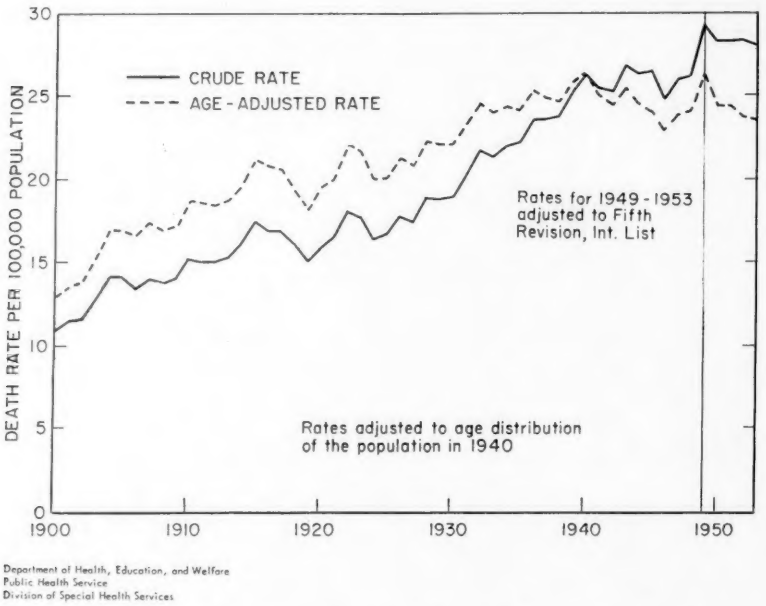
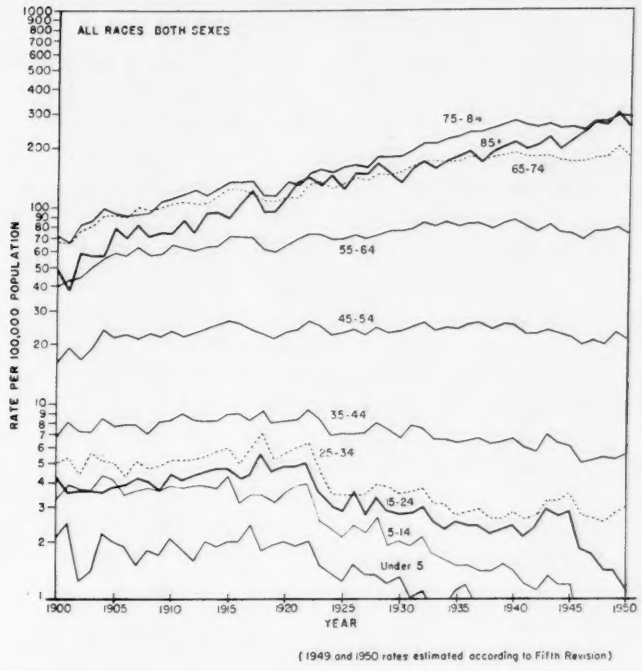


Fig. 5.—Crude and age-adjusted death rates from diabetes: United States Registration States, 1900-1953.

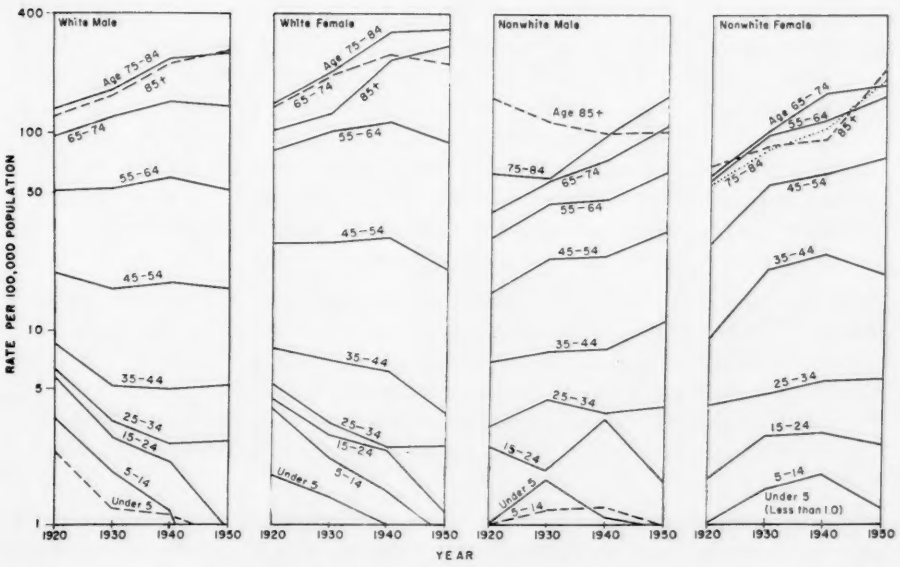
For trend purposes, rates for 1949 and succeeding years have been converted on the basis of comparability ratios, computed by the National Office of Vital Statistics, to estimates of what they would have been under the Fifth Revision of the International List. The relatively high diabetes death rate in 1949 may have resulted from the fact that not all states had introduced the new certificate in that year.

A factor which influenced the diabetes death rate in the 1940's was the withdrawal of large numbers of young persons, mostly males, from the population of the continental United States. Presumably the mortality rate from diabetes was lower in these persons overseas than in the persons remaining at home, resulting in artificial increases in the rate for the continental United States for the age group 15 to 34 for the war years.



(1949 and 1950 rates estimated according to Fifth Revision)

A.



(1950 rates estimated according to Fifth Revision)

B.

Fig. 6.—*A*, Death rates from diabetes mellitus by age: expanding death registration states, 1900-1932: continental United States, 1933-1950. *B*, Death rates from diabetes mellitus by age, race, and sex: expanding death registration states, 1920-1932: continental United States, 1933-1950.

TRENDS BY AGE, SEX, AND RACE

Trends in diabetes mortality can be seen most clearly when each age group is examined (Fig. 6, *A*). The mortality rates for children under 15 years have declined at a spectacular rate from 3.0 per 100,000 population in 1920 to 0.6 in 1948. Declines also appear in the other age groups up through 44. The 45- to 64-year group shows moderate declines since 1940; and from age 65 on, increases are evident. This pattern is true also of white persons, but is different for nonwhite persons, where in general rates have increased in persons over 25 (Fig. 6, *B*).

To what can this decline in diabetes mortality rates in white persons be attributed? First, the introduction of insulin in 1922 was followed by immediate reduction in the mortality rate of persons under 45. The life expectancy of diabetics was increased with death ensuing, in some cases from diabetes, in later years. By the late thirties and early forties, many persons whose lives were prolonged because of insulin in the twenties had died. Introduction of newer forms of insulin, better chemotherapy, and better medical management of the disease also must have played their part in the decline. The increased role of screening for diabetes should lead to even further declines in the years to come.

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TRENDS IN YEARS OF LIFE LOST

In Table IV, the number of deaths from diabetes and estimated potential years of life lost are shown by race and sex for the Registration States in 1920 and 1930 and for all states in 1940, 1948, and 1950. Consideration of the change from 1940 to 1948 (a period in which all the states were in the Registration area and during which the same method of classifying deaths was followed) indicates, in a small way, certain types of changes that apparently have characterized the entire period. Even in the eight years from 1940 to 1948, the number of deaths attributed to diabetes increased 10.3 per cent. The increase was greater for nonwhite than for white persons, the percentage increase in deaths being 18.7 for nonwhite males and 17.7 for nonwhite females.

Years of life lost because of diabetes increased only 8.5 per cent between 1940 and 1948. This percentage increase was less in years of life lost than in number of deaths for the total and for each race-sex group except nonwhite females, whose years of life lost showed an increase of 25.6 per cent. Years of life lost because of a specific condition are a function of the general mortality rate as well as the specific mortality rate, and the age at death from diabetes has increased considerably.

On the basis of the Fifth Revision of the International List of Causes of Death, somewhat over one-half million person years of life were lost because of diabetes in 1948. Over 300,000 of these were for white females. With the change to the Sixth Edition, the person years of life lost because of diabetes deaths in 1950 are estimated at over 360,000. Over one-half of these life years lost were for white females (over 200,000). The white females not only have a

high diabetes mortality rate, but also a high life expectancy, thereby increasing the life years lost.

TABLE IV. DEATHS FROM DIABETES AND ESTIMATED POTENTIAL YEARS OF LIFE LOST THROUGH DEATHS FROM DIABETES, BY RACE AND SEX, IN EXPANDING REGISTRATION STATES* 1920, 1930, 1940, 1948, AND 1950

RACE AND SEX	NUMBER OF DIABETES DEATHS						
	1920*	1930*	1940	1948	CHANGE 1940 TO 1948		1950†
					NUMERICAL	PERCENTAGE	
Total	13,898	22,345	35,015	38,638	+3,623	+10.3	24,419
White male	6,041	8,353	12,438	13,456	+1,018	+ 8.2	8,580
White female	7,282	12,490	20,168	22,339	+2,171	+10.8	13,567
Nonwhite male	262	551	782	928	+ 146	+18.7	768
Nonwhite female	313	951	1,627	1,915	+ 288	+17.7	1,504
	ESTIMATED POTENTIAL YEARS OF LIFE LOST‡						
Total	265,092	355,399	499,628	542,141	+42,513	+ 8.5	365,843
White male	125,008	129,661	167,802	174,860	+ 7,058	+ 4.2	118,885
White female	140,084	198,285	286,473	311,562	+25,089	+ 8.8	202,417
Nonwhite male	§	9,728	13,898	16,215	+ 2,317	+16.7	13,600
Nonwhite female	§	17,725	31,455	39,504	+ 8,049	+25.6	30,941

*Not all states were part of the Registration area in 1920 or 1930.

†The Sixth Revision of the International List of Causes of Death, which became effective in 1949, provides for coding the primary cause of death as specified by the physician, whereas, before, diabetes had priority over cardiovascular-renal diseases, for instance, which are frequently a late complication of diabetes. A 10 per cent sample of death certificates, double-coded in 1949 and 1950, indicated that only 57 per cent of the deaths which would have been coded as caused by diabetes under the Fifth Revision were so coded under the Sixth.

‡Based on life expectancy tables not eliminating diabetes as cause of death.

§Available data insufficient for estimating years of life lost in 1920.

TRENDS BY GEOGRAPHIC AREAS

Trends in diabetes crude mortality rates in the various geographic regions, in general, followed contours similar to those for the United States from 1930 to 1950. The Northeast Region at all times had higher diabetes death rates than the other regions. There was also a definite increase in rates in the Northeast Region from 1935 to 1940 and a very slight relative increase from 1940 to 1950. Rates in the North Central States showed increases from 1940 to 1950, but remained considerably below the level for the Northeastern States. The Southern and Mountain Regions showed increases throughout the period. In the Pacific States, there was a higher than average diabetes mortality rate in 1935, but between 1940 and 1950 there was somewhat of a decline.

Obviously differences and trends in regional rates are affected by differences and changes in age composition and other factors. Population changes during the war years make the calculation of regional rates in intercensal years extremely

difficult. However, using the census years of 1940 and 1950, we can compare the age-adjusted rates for the regions. In general, from 1940 to 1950 the greatest increase in the age-adjusted death rate from diabetes was in the Southern States, followed by the North-Central States. The Northeastern States showed little or no changes, and declines were evident in the Pacific and Mountain States, with the greatest declines in the Pacific States. In fact, in 1950 the age-adjusted rate for the Pacific States was approximately one-half that for the Northeastern States.

SUMMARY

1. In 1950, diabetes mellitus caused over 24,000 deaths (16.2 per 100,000 population).

2. The death rate from diabetes is highest in white females, followed by nonwhite females and white males. It increases with age in all groups and is higher in nonwhites than whites in early years of life but higher in whites from about age 65 on.

3. Mortality from diabetes is considerably higher in married women than in men or single women in the older age groups in which diabetes mortality is most significant. The rate in married men is also somewhat higher than in single men in these ages.

4. Deaths from diabetes are reported at a higher rate from urban than rural areas, but no association was found between rates and city size.

5. There is considerable variation from state to state and region to region in mortality rates from diabetes. In general, the Northeast and North-Central States have the highest rates and the South and West the lowest.

6. The trend of the number of deaths and crude death rates from diabetes has been upward since 1900 with a tendency to level off in recent years. Rates for children under 15 have decreased considerably from 1920, with lesser, but continuous, declines in all age groups up to 45.

7. The trend in years of life lost has been upward, but at a less steep rate than the trend in deaths due to the increasing age at death from diabetes. In 1950, there were approximately 366,000 years of life lost because of diabetes, of which over 200,000 were for white females.

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THE ETIOLOGY OF NONGONOCOCCAL (NONSPECIFIC) URETHRITIS*

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IN THE venereal diseases clinics of England and Wales in 1952 there were 11,552 cases of nongonococcal urethritis as compared with 15,510 male cases of gonorrhea (Ministry of Health, 1953). In the previous year there were 10,794 cases as compared with 14,975 cases of gonorrhea.

Although the condition has been known for many years, it was finally clearly focused during World War II, as in British Military venereal diseases hospitals thousands of early morning smears were examined for the gonococcus and found wanting (Willcox, 1949). Although a few then still regarded the disease as due to chronic gonorrhea, it was generally accepted as a separate entity (McElligott, 1942). Its first impact on the American scene was reported from the Pacific theater, where the condition was commoner than gonorrhea (News and Comment, 1947) and it later became a considerable problem among United States forces occupying Japan where, in the United States Air Force, there was an incidence of 12.9 cases per 1,000 (Baier, 1949). The disease attracted further attention as these men returned to the United States (Crouch, Reese, and Boudreau, 1953), since which time the condition has proved troublesome among United States servicemen in the United States (Graham, 1952).

Today there is little doubt as to the seriousness of the problem, which is aggravated by an acute awareness of the unsatisfactory state of our knowledge as to its etiology. This lack has so far prevented any epidemiologic and social action being taken with confidence. Even so, in the United States, there is still a minority who do not consider that the evidence that the disease is necessarily venereal is entirely convincing (Ambrose and Taylor, 1953; Breakey, 1953). Although few in Great Britain doubt that it is venereal, the fact that anyone at all should have misgivings only serves to weaken the conviction of the necessity to take epidemiologic action such as the examination of contacts. Also, the laws and regulations of most nations concerning the venereal diseases were framed to embrace syphilis and gonorrhea at a time when nonspecific urethritis as a problem was not envisaged, and this also makes effective epidemiologic planning the more difficult.

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It is thus of paramount importance that the causative organism of nonspecific urethritis be discovered without delay, for on the results of this basic research depend all measures aimed at the effective control of the disease. That nongonococcal urethritis can be evoked by a multiplicity of causes is well known, and whole books have been written about them (e.g., Harkness, 1950). It is, however, reasonable to suppose that in common practice there is a single cause for the majority of cases.

In recent years attention has principally been concentrated on five possible causes: (1) bacteria, (2) trichomonads, (3) spirochetes, (4) pleuropneumonia-like organisms, and (5) viruses (Willcox, 1953).

(1) *Bacteria.*—Nonspecific urethritis has traditionally been classified into bacterial and abacterial urethritis, according to whether bacteria can be seen in the smears, the bacterial group consisting of about one-quarter of cases. The bacteria found have included a wide variety of conventional organisms. Latterly, however, it has been shown by cultural methods that the same organisms can be grown from the abacterial forms.

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TABLE I. URETHRAL CULTURES

ORGANISMS	CONTROLS* (105 CULTURES)		NONSPECIFIC URETHRITIS CASES			
			BEFORE TREATMENT (81 CULTURES)		AFTER TREATMENT (69 CULTURES)	
	NO.	%	NO.	%	NO.	%
Staph. albus	72	68.6	66	81.4	55	79.7
Escherichia coli	22	21.0	16	19.7	9	13.0
Diphtheroids	19	18.1	26	32.1	27	39.1
Saprophytes	8	7.6	4	4.9	9	13.0
Staphylococcus aureus	4	3.8	1	1.2	—	—
Monilia	3	2.8	1	1.2	1	1.4
Proteus group	—	—	—	—	1	1.4
Enterococci	—	—	2	2.5	—	—
Streptococci	—	—	1	1.2	2	2.9
Sterile	2	1.9	1	1.2	3	4.3

*Substantially the same results were obtained in forty-six control cultures repeated one week or more later.

In a series of eighty-one urethral cultures made on my own nonspecific urethritis cases before treatment, of sixty-nine urethral cultures made after treatment, and of 105 on controls, it was evident that there was little difference in the patterns of the three series and that the organisms found were usually commensals (Table I). The urethral *Staphylococcus albus* was the organism most commonly seen (Willcox, 1954). Moreover in United States forces in the Far East a Staphylococcus of varying sensitivity was found in 60 to 65 per cent of cases (Gartman and Leibovitz, 1952). In the United States, Ambrose and Taylor (1953) likewise isolated a variety of organisms in the lower genitourinary tract of both patients and controls, but there was nothing to suggest that any of

the organisms found were connected with the etiology of nonspecific urethritis; as in my own series, sterile cultures were seldom encountered.

Recently it might be added that Ambrose and Taylor (1953) have reported the presence of small coccobacillary organisms in cases of nonspecific urethritis but not in controls, which were considered to merit further study. Also Leopold (1953) has reported a gram-negative, nonmotile, noncapsulated pleomorphic Bacillus with a tendency to form hemolytic colonies, apparently related to the genus Hemophilus, which was also believed to have some relation to nonspecific urethritis.

(2) *Trichomonads.*—Certainly the more frequently that dark-field tests are performed on the discharges of nonspecific urethritis, and the longer that the specimens are examined, the more often will trichomonads be found. Thus in recent years Lanceley (1953) found *Trichomonas vaginalis* in 5.3 per cent of 310 cases, and Sorel (1952) in 10 per cent; higher rates of up to 29 per cent have been recorded (Harkness, 1950). Even so there is still far from sufficient evidence that *T. vaginalis* is responsible for the bulk of cases of nonspecific urethritis seen. An important recent observation has been made by Lanceley and McEntegart (1953), who inoculated intraurethrally with cultures of *T. vaginalis* five male volunteers, all of whom developed some urethritis and in three of whom trichomonads could be demonstrated. Five controls inoculated with sterile culture medium had no such reaction. This aspect of the problem certainly deserves further research.

(3) *Spirochetes.*—Following the demonstration of spirochetes in the urine in cases of so-called abacterial pyuria (Coutts and Vargas-Zalazar, 1946), and noting the association of this condition with a urethritis (Horne, 1953), some workers have pursued the theory of a spirochetal cause of nonspecific urethritis based on the finding of spirochetes similar to those found in the mouth. It has been suggested in consequence that the practice of anal coitus or fellatio may be responsible (Coutts, 1948). Fifty patients with nonspecific urethritis and 100 other patients attending the venereal diseases clinic were therefore questioned concerning the practice of oral and anal intercourse, but it was evident that there was no higher incidence of such sexual variants in the nonspecific urethritis group (Table II). Thus, as far as Great Britain is concerned, these practices play little part in the etiology of the condition.

TABLE II. TYPE OF LAST INTERCOURSE OF PATIENTS ATTENDING A VENEREAL DISEASES CLINIC FOR THE FIRST TIME

	CASES	"NORMAL" INTERCOURSE	ORAL INTERCOURSE	RECTAL INTERCOURSE	% UNUSUAL INTERCOURSE
Nonspecific urethritis patients	50	47	2	1	6.0
Other patients attending venereal disease clinic	100	91	5	4	9.0

(4) *Pleuropneumonia-like Organisms.*—Upon the discovery that pleuropneumonia-like organisms would cause arthritis and conjunctivitis in rats (Findlay, 1946), the possibility that they might be the cause of Reiter's syndrome and therefore some cases of nonspecific urethritis had to be investigated. (Incidentally we are still in the dark as to whether the Reiter complex is a separate disease or whether most cases of nonspecific urethritis are, under certain unknown circumstances, susceptible to it.) Pleuropneumonia-like organisms have repeatedly been demonstrated in a considerable proportion of males with nonspecific urethritis (Harkness and Henderson-Begg, 1948; Melén and Linnros, 1952); and although the first-named workers stated them not to be present in fifty normal controls, they have since been demonstrated in males and females attending urology clinics (Morton and others, 1951), and in significant numbers in healthy men (Nicol and Edward, 1953), in healthy women (Melén and Odeblad, 1952), in throat cultures (Smith and Morton, 1951), and even in the saliva of normal persons (Morton and his associates, 1951a). The current view is that they are unrelated to nonspecific urethritis and are commensals (Edward, 1952; Nicol and Edward, 1953; Wagner, Morse, and Kuhns, 1953). Recently Keller and Morton (1953) have shown that pleuropneumonia-like organisms are highly resistant to erythromycin, although unpublished personal studies indicate that this antibiotic has some definite beneficial action in the treatment of nonspecific urethritis.

(5) *Viruses.*—The presence of blue-staining inclusion bodies and fine red granules apparently within the cytoplasm of epithelial cells and also lying free was described in trachoma by Halberstaedter and von Prowazek in 1907. Similar bodies have since been reported in a number of established virus diseases to which the generic term "Chlamydozoaceae" has been applied. From time to time numerous authors have noted similar inclusions in conjunctival scrapings from cases of so-called inclusion blennorrhea and also from urethral scrapings in cases of nonspecific urethritis. Others have disagreed, particularly concerning the latter. The whole matter was well reviewed by Harrison and Worms in 1939. It has been suggested that these bodies represent stages in the life cycle of a virus of the lymphogranuloma venereum-trachoma-psittacosis group. A similar virus producing similar bodies is apparently responsible for enzootic abortion in ewes (Stamp, 1951).

Such inclusions were reported in the urethral scrapings of many cases of primary nongonococcal urethritis and in the urethra and conjunctiva in seven cases of Reiter's disease by Harkness in 1944 (quoted in his book [1950], p. 681). Durel and his associates (1951) found either the chlamydozoon or pleuropneumonia-like organisms in eight of sixteen cases, and they were also reported by Willcox and Findlay (1952). Durel and Borel (1951), however, considered that virus inclusions were less frequently responsible for nonspecific urethritis than pleuropneumonia-like organisms, while Bedson (1950) could find no evidence of the virus of inclusion blennorrhea in 25 persons with nonspecific urethritis tested.

It was thought worth while, therefore, to try by different means to accumulate additional evidence for or against a virus etiology of the condition, (a) by

means of skin and (b) by means of complement fixation tests using antigens of the lymphogranuloma venereum-psittacosis-trachoma group of viruses; (c) by a large-scale examination of Giemsa-stained urethral scrapings; and (d) by animal and egg studies.

(a) *Skin Tests.*—The results of the skin tests are shown in Table III. In all, 234 skin tests were performed, 175 for lymphogranuloma venereum, twenty-eight for psittacosis, and thirty-one for cat-scratch fever, but repeated tests on the same patients have been omitted from the table.

TABLE III. SKIN TESTS

	TESTED	NEGATIVE	DOUBTFUL	POSITIVE	% POSITIVE
Lymphogranuloma venereum:*					
N.S.U. cases	84	63	10	11	13.1
Controls	62	53	6	3	4.8
Psittacosis:†					
N.S.U. cases	17	15	2	—	—
Controls	11	11	—	—	—
Cat-scratch fever:‡					
N.S.U. cases	16	12	2	2	12.5
Controls	12	12	—	—	—

Antigens kindly supplied by:
*E. R. Squibb and Sons, International Corporation, New York ("Lygranum"), and Virus Reference Laboratory, Colindale.
†Virus Reference Laboratory, Colindale (courtesy of Dr. A. D. Macrae).
‡Professor P. Mollaret, Hôpital St. Bernhard, Paris, and Virus Reference Laboratory, Colindale (courtesy of Dr. H. J. Bensted).

The tests for psittacosis gave entirely negative results both in nonspecific urethritis cases and in controls, but there was apparently a slightly increased incidence of positivity in cases of nonspecific urethritis or their consorts tested against lymphogranuloma venereum with Lygranum antigen over results in controls. (Ambrose and Taylor [1953] reported negative Frei tests in forty-five cases of nonspecific urethritis, using an unspecified antigen.) Similar findings were noted with cat-scratch antigen and this matter, therefore, would also seem to require further investigation.

(b) *Serum Tests.*—Four hundred twelve complement fixation tests for lymphogranuloma venereum (Macrae and Willcox, 1953) were made on 127 persons who had or had had nonspecific urethritis or Reiter's syndrome, on fourteen of their female consorts, and on 132 controls. A further series of 323 complement fixation tests for enzootic abortion in ewes, a veterinary disease considered to be due to a virus of the lymphogranuloma venereum-psittacosis group, were made on 115 males with present or past nonspecific urethritis and Reiter's syndrome, on eight female consorts, and on 127 controls (Willcox and Stamp, 1954).

No significant differences were noted in either test as between the nonspecific urethritis and control groups, and no significant increases in titer were observed with repeated tests or according to the duration of symptoms at the time that the tests were made. The results of the first tests taken in each patient are summarized in Table IV. In 263 instances the same specimen of blood was subjected to the two tests and the results, given in Table V, showed a very high measure of agreement.

TABLE IV. SERUM TESTS (FIRST TESTS ONLY)

	TESTED	NEGATIVE	DOUBTFUL	POSITIVE	% POSITIVE
Lymphogranuloma venereum:					
N.S.U. cases	141	122	13	6	4.3
Controls	132	120	9	3	2.3
Enzootic abortion in ewes:					
N.S.U. cases	123	113	6	4	3.2
Controls	127	118	4	5	3.9

TABLE V. COMPARISON OF LYMPHOGRANULOMA VENEREUM AND ENZOOTIC ABORTION IN EWES COMPLEMENT FIXATION TESTS

TITERS	1/10 OR BELOW	1/20	1/40 OR OVER	TOTAL E.A.E.TESTS
1/4 or below	218	15	—	233
1/8	1	10	8	19
1/16 or over	1	3	7	11
Total L.G.V. tests	220	28	15	263

(c) *Giemsa-Stained Urethral Scrapings.*—Some 1,463 Giemsa-stained scrapings, taken from patients with nonspecific urethritis, their female consorts, or from controls, were examined by one person using the same technique: 805 specimens were taken from 250 male cases of nonspecific urethritis before or after treatment, 344 specimens were taken from 45 female consorts, and 314 specimens were taken from 251 controls.

In order to determine the significance or otherwise of the various bodies seen, in a manner which would embrace virus inclusions, elementary bodies, and pleuropneumonia-like organisms, the results were classified in the course of the investigation according to whether blue or red granules or blue or red "colonies" (the latter being granular bodies varying from 1 to 6 μ in diameter) were seen in the cytoplasm of the epithelial cells or lying free. The incidence of the various bodies noted was compared in male patients with nonspecific urethritis before treatment, after successful treatment with the orally administered antibiotics, and after unsuccessful treatment (Table VI).

It will be at once noted that the incidence of the red "colonies" and red granules was unaffected by the outcome of treatment and that these, therefore,

are unlikely to have been connected with the disease. On the other hand, the incidence of blue "colonies" and blue granules fell significantly after successful treatment but remained high when the treatment was unsuccessful. At the time of re-treatment given in forty-two untabulated cases, the incidence of blue "colonies" had risen 30.9 per cent and of blue granules to 23.8 per cent, figures comparable to those obtained before treatment.

TABLE VI. INCIDENCE OF VARIOUS BODIES IN GIEMSA-STAINED URETHRAL SCRAPINGS FROM MALE PATIENTS WITH NONSPECIFIC URETHRITIS

	BEFORE TREATMENT (206 CASES)		AFTER SUCCESSFUL TREATMENT (182 SCRAPINGS)		AFTER UNSUCCESSFUL TREATMENT (103 SCRAPINGS)	
	NO.	%	NO.	%	NO.	%
Blue colonies	71	34.5	18	9.9	23	22.3
Red colonies	17	8.3	15	8.2	6	5.8
Blue granules	36	17.5	15	8.2	17	16.5
Red granules	38	18.4	42	23.1	24	23.3
Nil	78	37.9	115	63.2	50	48.5

A control group of eighty, consisting of twelve specimens of nonurethral pus, urethral scrapings from eighteen normal males, from thirteen patients attending the venereal diseases clinic because of fear of venereal disease, from seventeen patients with syphilis, and from twenty patients with genital lesions of a nonsyphilitic character, was next examined. In only two (2.5 per cent) were blue "colonies" and in only one (1.25 per cent) were blue granules discovered (Table VII). Up to this point the investigation showed considerable promise as far as the blue "colonies" and blue granules were concerned.

TABLE VII. INCIDENCE OF VARIOUS BODIES IN CONTROLS

NATURE	NO. CASES	BLUE "COLONIES"	RED "COLONIES"	BLUE GRANULES	RED GRANULES	NIL
Nonurethral pus	12	0	0	0	0	12
"Normal" males	18	0	0	0	0	18
Anxiety cases	13	1	1	1	—	10
Syphilis cases	17	—	1	—	—	16
Patients with nonsyphilitic genital lesions	20	1	2	—	1	16
Totals	80	2	4	1	1	72
%	100	2.5	5.0	1.25	1.25	90.0

It was appreciated, however, that one essential difference between the nonspecific urethritis cases and the controls was that the latter had dry urethras

whereas the former had not, and that possibly the bodies seen were merely products of inflammation. A further control series of 108 male patients with untreated gonorrhea and treated with penicillin at various lengths of time previously was therefore studied. In these, fifteen (13.9 per cent) showed blue granules; and as this incidence was nearly as high as the 17.5 per cent found in untreated nonspecific urethritis, it was evident that these too could be discounted. The incidence of blue "colonies" was 14.8 per cent, a figure still substantially below the 34.5 per cent found in patients with untreated nonspecific urethritis.

When the results in the gonorrhea cases were arranged according to the length of time which had elapsed since the giving of the penicillin and the taking of the scraping, however, it was noted that the incidence of blue "colonies" at 1 to 3 days was 21.7 per cent (Table VIII), which was not far removed from the 27.6 per cent incidence 2 to 7 days after the onset of treatment of nonspecific urethritis with one of the orally administered antibiotics (Willcox, Howard, and Findlay, 1954). It is therefore regretfully concluded that none of the bodies studied in this investigation was concerned with the causation of nonspecific urethritis.

(Note: For reasons of clarity a consideration of the specimens from females has been omitted from this report.)

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TABLE VIII. INCIDENCE OF BLUE COLONIES IN A FURTHER CONTROL SERIES OF GONORRHEA CASES

TIME SINCE TREATMENT	CASES	BLUE COLONIES	%
Untreated	23	2	8.7
1-3 days	46	10	21.7
4-7 days	24	4	16.6
Over 7 days	15	—	—
Total	108	16	14.8

Incidence in Nonspecific Urethritis Cases

Before treatment	34.5%
2-7 days from outset of treatment	27.6%
After successful treatment	9.9%

Animal Experiments.—Attempts to transmit the virus of nonspecific urethritis into the lungs and brains of mice. into the conjunctiva, urethra, and knee joints of baboons, subcutaneously into guinea pigs, and into the chorioallantoic membranes of hens' eggs in experiments involving some 1,735 mice, 100 eggs, in addition to a few guinea pigs and baboons, were entirely unsuccessful (Willcox and associates, 1954).

SUMMARY AND CONCLUSIONS

1. It is now appreciated that nonspecific urethritis is a world problem of considerable magnitude.

2. Its etiology remains obscure. Five possible causes, namely, bacteria, trichomonads, spirochetes, pleuropneumonia-like organisms, and viruses are considered.

3. In a study of 301 urethral cultures taken from nonspecific urethritis cases before and after treatment, or from controls, no significant differences were noted, and bacterial urethritis is not considered to be the common entity.

4. The incidence of buccal or anal coitus was no higher in nonspecific urethritis than in other patients attending the venereal disease clinic.

5. Attempts to prove or disprove a virus etiology were made by a study of 234 skin tests for lymphogranuloma venereum, psittacosis, and cat-scratch fever; 412 complement fixation tests for lymphogranuloma venereum; and 323 complement fixation tests for enzootic abortion in ewes on nonspecific urethritis patients, their female consorts, or controls. Some 1,463 Giemsa-stained scrapings were also examined, and animal experiments involving 1,735 mice, 100 eggs, and a few baboons and guinea pigs in addition have been summarized.

6. Skin tests for lymphogranuloma venereum and cat-scratch fever showed more positive results in the nonspecific urethritis cases than in controls and this would appear to merit further attention. No significant differences were noted between the nonspecific urethritis cases and controls in the results of the complement fixation tests for lymphogranuloma venereum or for enzootic abortion in ewes.

7. The Giemsa-stained urethral scrapings were classified according to whether blue "colonies," blue granules, red "colonies," or red granules were seen in the smears. No significant differences were noted in the incidence of red "colonies" or granules before or after successful or unsuccessful treatment with the orally administered antibiotics, and these were therefore ignored. The blue "colonies" and blue granules, on the other hand, had a relatively high incidence before treatment, a low incidence after successful treatment, and a high incidence after unsuccessful treatment. Moreover the incidence of both was negligible in controls.

8. Since the controls had dry urethras, a further control series with wet urethras, consisting of gonorrhea patients previously treated with penicillin, was next taken. It was found that the incidence of blue granules in these cases was high and they too were discounted. When the gonorrhea cases were arranged according to the time since the administration of penicillin, it was noted that at 1 to 3 days the incidence of blue "colonies" was high, and it was regretfully concluded that none of the bodies studied was concerned with the etiology of nonspecific urethritis.

9. All attempts to passage the virus into the brains or lungs of mice, subcutaneously into guinea pigs, or into the conjunctiva, urethra, or knee joints of baboons, were a failure, as were inoculations into embryonated hens' eggs.

10. The cause of nonspecific urethritis still remains to be discovered.

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The Giemsa-stained urethral scrapings were examined by Miss E. M. Howard, and the animal experiments conducted by Dr. G. M. Findlay, both at the Laboratories of the School of Pharmacy, London, through the courtesy of Professor G. A. H. Buttle.

The urethral cultures were made by Dr. E. Sayle, King Edward VII Hospital, Windsor, England.

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EXPERIENCE IN PROVIDING CARE FOR THE LONG-TERM PATIENT AND THE LIGHT IT THROWS ON ADDITIONAL RESEARCH NEEDED*

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THE purposes of this review are:

1. To give illustrative examples of the extent to which available information provides knowledge of disease conditions; the population groups involved; the goals for rehabilitation suitable for a given program; the staff, facilities, and financial resources needed; and the results to be anticipated for patients, their families, and the communities in which they live.

2. To point to the kinds of additional information required for better understanding of the problems of long-term patients and for more effective efforts to meet their needs. We have not attempted here to indicate specific studies or the priorities that should be assigned to such studies, or to describe the methodological principles to be employed.

The experience analyzed is presented later in three major sections: the patient at home; the patient in an institution; and integration of services and facilities. Limitations of time precluded collecting and reviewing existing sources of data on financing.

This review is limited to reports pertinent to our present purpose, published in this country and in Great Britain. Most reports of experience in operating programs for the chronically ill have been included in *Chronic Illness—Digests of Selected References*[59] and its 1950-1952 supplement[60]; the reader may refer to these digests for summaries of these and for additional references to surveys.

THE PATIENT AT HOME

The rapid and continued increase in the use of hospitals for the care of illness, and the waiting lists for admissions to general hospitals and to institutions for prolonged care of aged, infirm, tuberculous, or mentally deranged patients, have given new impetus to efforts to provide appropriate services to people in their own homes. Organized arrangements have therefore been made in many

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communities to provide home services which can offer satisfactory care to ambulatory and even bedfast patients. It is claimed that home services can often avoid the necessity for admission to an institution and, in many instances, can help the patient to adjust more quickly to his customary family and community life than if he is forced to spend a long period in an artificial and often costly environment.

The organized programs for care of patients at home cover one or more of a wide range of services: home nursing as an adjunct to physician visits, housekeeping help, dietary instruction, loan or other provision of sickroom equipment and appliances, social case-work services, and physical and occupational therapy.

Goldman[34] has advocated making home care an integral part of any program of medical care. He outlined as prerequisites a suitable physical environment in the patient's home, favorable psychologic attitudes in both patient and family, suitability of the patient's illness to this type of care, and proper organization and supervision of the service. Determination of the feasibility of home care should be made by a physician in cooperation with a social worker and a visiting nurse. Participation in the program should be open alike to approved hospitals, clinics, physicians in private practice, and public and private social agencies.

What is the existing experience on the sponsorship, scope, and administration of home care programs? A few examples will indicate their diversity.

Bellevue Hospital in New York City[1] has a home care program available for patients who pay no more than $2.00 a day for hospital care. It is designed for an ultimate case load of 200 patients, and is staffed by 6 assistant resident physicians, 4 physical therapists, 4 occupational therapists, social workers, a nurse coordinator, and clerical personnel. Nursing services are provided by a visiting nurse association.

The Boston University School of Medicine[5] operates a program for a low-income population of about 50,000 persons. Senior medical students provide medical services under the supervision of the residents and staff of the Department of Preventive Medicine. Bedside nursing is supplied by the visiting nurse association, and social services are furnished by the Massachusetts Memorial and Boston City Hospitals. Patients receive hospital care in the wards of these hospitals when necessary. About one-half the patients served in 1950 were under age 5. The predominant need for bedside nursing and social services, however, was in the age groups over 40.

A program in Philadelphia is administered by the visiting nurse association assisted by a steering committee composed of representatives of community agencies and of cooperating hospitals.[61] The staff includes a physician serving part time as medical director, a full-time nurse coordinator, and a part-time secretary. The patient remains under the care of his private physician and receives the services of visiting nurses, physical and occupational therapists, and housekeepers, as needed. Patients pay one-half the costs of home care services while one-half is borne by the community. Of a total of 120 patients of 95 physicians served in the first thirty-two months of operation, nearly one-half were aged 65 or over. Of the patients, 84 per cent needed nursing care, 62 per cent physical therapy, 28 per cent case-work services, 33 per cent housekeeping services, and 3 per cent speech therapy.

Stimson[58] advocated home care of patients with acute poliomyelitis when proper management is possible and no threat to life is feared. Trimble[58] has found home care for tuberculosis patients a solution to many of the problems of preventing invalidism and of reducing pressure on the hospitals. The potentialities for home care in tuberculosis control have been further enhanced recently as a result of favorable findings obtained when chemotherapy is given to ambulatory patients.

The feasibility of home services as a substitute for or supplement to care in an institution depends on the medical needs and infirmity of the patient, the suitability of his home, the presence of relatives or friends to give the supervision and domestic service necessary, and the assurance that prompt admission or readmission to an appropriate institution can be effected when the need arises.

Since many of these factors must be considered regardless of the scope of the home services provided, our attention is given first to information on type of patient, home, family, and community that have been regarded as suitable for home care. Thereafter some of the data available on services included in organized home care programs will be outlined.

The Suitable Patient.—The question as to whether the patient's condition requires care in some institution is answered by the complexity, frequency, and continuity of the medical and professional nursing supervision he must have, and the likelihood of frequent or suddenly emergent need for surgical procedures or for the use of a hospital's equipment for diagnosis or treatment.

The potentialities for home care programs are revealed by studies of the medical and nursing needs and the period of bedfast convalescence of patients discharged from hospitals; by surveys of medical needs of population groups, particularly those on waiting lists for admission to an institution; or by surveys of the capacity for self-care in groups of assistance recipients or persons in nursing homes.

The Syracuse University Hospital,[35] before starting its home care program, made a twelve-month study of discharged patients. This revealed that about 90 per cent of the costs of hospitalization on the general wards was for chronic illness. Only one-third of the discharged patients were found to have received satisfactory medical supervision after leaving the wards. The effect was then estimated of adequate medical supervision after discharge in shortening the duration of hospital stay and reducing readmission rates.

Similarly, a hospital management committee in Paddington, England,[38] had a physician visit the homes of applicants on a waiting list for hospital admission. He found that 32 per cent of the applicants did not need hospital care but were in need of such services as home nursing, domestic help, outpatient care. Of the 28 per cent who needed institutional care, one-half could have been cared for in long-stay annexes to the hospital if such facilities had been available. The remaining 40 per cent of the applicants had made other arrangements or had died. The need for institutional care other than hospitalization largely arose from the fact that home conditions were often unsanitary, crowded, and otherwise unsuitable.

Studies of the degree of infirmity of a group to be considered for a home care program can also reveal the extent to which that program should be integrated with other provisions for medical, nursing, and auxiliary services. Analysis of the characteristics of persons receiving state-Federal aid to the disabled,[62] for example, indicates that 25 per cent lived alone, 58 per cent lived with relatives or other persons, and 17 per cent lived in institutions or elsewhere. In all, 21 per cent were confined to the house; 8 per cent needed help of others in outside activities. Heart disease was the major impairment of 25 per cent, while 11 per cent were disabled by paralysis, 10 per cent by arthritis, and 7 per cent by mental conditions.

The Source Book on Size and Characteristics of the Problem of Care of the Long-Term Patient[46] carries in Tables 12, 13, and 14 summary data from this study of recipients of aid to the permanently and totally disabled. The *Source Book* also gives data on mental condition, bed status, ability to walk, and other characteristics of patients served by the Baltimore City Instructive Visiting Nurse Association (Table 22) and of patients in nursing care institutions in Maryland (Tables 45-47).

Such studies add greatly to the experience on which others may draw in planning programs for their own communities. They need supplementation, however, if they are to characterize the disease conditions that require services, the types of services needed, and the criteria to be used in determining either. Lacking, also, are data on the frequency of use of surgical procedures and hospital equipment for patients of different diagnostic categories, the association of such use with nursing services, and the expected frequency of emergencies that may arise for hospital diagnosis and treatment.

The Suitable Home.—Each disease, of course, may require certain conditions of the home to meet standards of suitability. For infectious tuberculosis, for example, a home care patient should have a room to himself to safeguard against infection of other persons in the family. Accessibility and adequacy of toilet and cooking facilities must also be considered in the care of patients at home. Moreover, steep stairs, narrow doors and halls, and congested living quarters may prevent the wheel-chair patient from participation in family life and impose difficulties in providing essential care.

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Many decisions regarding the suitability of a home can be made only on an individual basis for individual patients. They depend in many instances on the way of life the patient and his family find comfortable and satisfying. Nevertheless, studies are needed to determine the factors in living arrangements that have a bearing on the type and objectives of the program being considered. Data are needed, for example, on housing conditions favorable or unfavorable for heart disease, rheumatic conditions, and other disabling impairments.

From the standpoint of developing communitywide programs, collection and analysis of data on housing for the various areas of the community will give useful information on the prevalence of walk-up, multifamily dwellings, the average number of persons per room, presence or absence of inside toilets, equipment of kitchens, and heating and lighting arrangements. A study of the homes and living arrangements of patients in hospitals, on waiting lists for admission to sanatoriums, or on visiting nurse case loads can also supply valuable information on the suitability of living arrangements. Such data, however, are most useful when the criteria for a suitable home can be related to factors known to be important for specific disease conditions and for patients with specific limitations of mobility and capacity for self-care. Patterns of needs and resources can thus be determined.

The Suitable Family.—Aside from the medical needs of the patient and the conditions of the physical environment conducive or detrimental to therapy and rehabilitation in the home, there is the important question of the patient's family. The patient needs sympathetic and cooperative care of a responsible person in the household during his disabling illness, while also his family needs protection against complete disruption of family life.

Analysis of the living arrangements of persons on waiting lists for admission to hospitals, tuberculosis sanatoriums, nursing homes, and homes for the aged indicates the extent to which applicants have relatives, friends, or other resources to provide the supervision needed in a home care program. A study of aged applicants for admission to St. Pancras Hospital in London[31] not only showed the suitability or unsuitability of the home for home care services but also revealed

the presence or absence of responsible persons in the household or neighborhood who could be relied upon to aid the patient when necessary. Of 215 persons visited, 98 lived alone, receiving a little help or none at all from neighbors and friends. Of 172 admitted to the hospital, 124 were chronically ill. The reasons for admission were not medical alone but included illness of the relative giving care, squalor and neglect, progressive deterioration of the patient, and development of an acute complication.

Foster home care and the provision of homemaker service have been used as substitutes for suitable homes and families. Thus the Bi-Regional Conference on Long-Term Care of Ill Children in Arizona[9] advocated foster home care, particularly for children under age 6, when home care was impossible, on the ground that the patient's requirements for personal warmth and response can be met more satisfactorily than in an institution. A study in New York State[28] revealed that foster home care for selected mental patients promoted satisfactory adjustments to life outside an institution. Homemaker service, according to the National Conference of Social Work,[47] prolongs the period during which infirm aged persons can continue to remain at home.

For what disease conditions are foster home care and homemaker services most suitable? What are the costs? How should the arrangements be organized and administered? These questions can be profitably studied to provide guides to the development or expansion of programs to provide these substitutes for a suitable home.

The Suitable Community.—Organized programs for care of the patient at home have been developed in relatively compact urban areas, and many serve only sections of those areas within fairly close proximity to the center from which the home services radiate. Are these services equally appropriate for rural areas? This question requires study of the cost and professional time spent in transportation, and the frequency of home visits required for given categories of patients in home care programs that cover a wide geographic area, rural as well as urban.

Questions arise also concerning the need for special consideration of cultural and language differences among population groups within a community. Impediments in communication as well as in transportation may prevent the effectiveness of a program. In research designed to appraise that effectiveness it is necessary to take account of social factors which may distort the findings, or indicate the need for a staff familiar with the customs and speech of the different ethnic groups that make up a heterogeneous population. Research, for example, can help us determine whether what looks like resistance, lack of cooperation, or even ignorance stems from faulty understanding or conflict with mores. For such research in particular there is need to utilize the skills and knowledge of the behavioral sciences.

Pattern of Payment.—In the main, organized provisions for services in the patient's home have been developed for the indigent or medically indigent. Are they equally appropriate for higher-income groups on a pay or part-pay basis? Can prepayment schemes be developed for such services? These questions have been raised time and again, but no specific information has been published.

Services and Personnel.—As indicated previously, there is considerable variation in the scope of organized home care programs for long-term patients; to date, only a few programs have been developed with the hospital as a center.

This variation is reflected in the information available on the purpose, extent, and volume of services provided in these programs, and on the personnel involved. The following section summarizes this information as it concerns medical, nursing, homemaker, social case-work, and rehabilitation services in the several kinds of home care programs discussed.

Medical services: Varieties of experience in the provision of physicians' services in home care programs have not been described in the literature, except in relation to the use of home care as a part of the training of medical students.

Data are lacking on the types and frequency of physician services needed in programs for various age groups, disease conditions, and severity of illness; on the training and qualifications of physicians who serve home care programs; and on the use of diagnosticians, consultants, and specialists.

Nursing services: Adequate information on the total extent of visiting nurse activities by public and private agencies is lacking. Data are not available on the variety of arrangements between local public health departments and voluntary organizations whereby their activities are integrated.

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According to Tables 24 and 25 in the *Source Book*[46] cited earlier, 91 cities of 100,000 population and over reported visiting nurse associations as separate organizations or in combination with some other agency. The V. N. A. organizations in 129 cities, including those of less than 100,000 population, reported a total of nearly 160,000 visits to chronically ill patients in a month of 1951, or more than one-half of their monthly total of about 302,000 visits.

Clark, describing the Health Insurance Plan of Greater New York,[44] showed how nursing services from the V. N. A. are used by a prepayment health program. In 1950 the utilization of the services was at a rate of 40 nursing visits per 1,000 persons enrolled. At a subsequent rate of 59 visits per 1,000 people per year, the cost of the visiting nurse service is about 15 cents a year per person insured. These visits include home nursing services for all types of illness, not merely those for chronic conditions.

Some data are available on nursing services for the chronically ill. For example, when maternity and communicable disease patients were excluded, heart disease and other circulatory disorders accounted for nearly 40 per cent of the patients served by the V. N. A. in Baltimore City in a four-week period in 1953 (*Source Book*,[46] Table 28). More than one-half the patients served had been receiving the service for three months or more. Bed baths and hypodermic injections each accounted for slightly more than one-third of the nursing services given. About one-fifth of the patients had not seen a physician for one month or more.

Beers,[7] writing of V. N. A experience in Allegheny County, Pennsylvania, emphasized the increase in the proportion of chronic disease patients from 15 per cent of the total case load and 40 per cent of the visits in 1949, to 18 per cent and 47 per cent, respectively, in 1951. She urged an active community program for the chronically ill to include more adequate medical care in the home and the employment of practical nurses as assistants to the V. N. A. Similar recommendations for use of practical nurses under the supervision of a public health nurse were made by Bortz[15] in 1948.

Indicating that current concern with chronic illness dictates a review of the role of the public health nurse, Reeve[49] recommended provisions to enable the nurse to draw on all possible community resources to meet the patient's total need; and described a V. N. A. consultant committee in New Haven, Connecticut, to advise on mental hygiene, nutrition, social work, orthopedics, and tuberculosis.

Recently collected data indicate that some 33 visiting nurse organizations (including local health departments) give physical therapy services in addition to nursing (*Source Book*,[46] Table 26). Seventeen such agencies give nutrition services, 9 give social service, and 3 give occupational therapy. Analysis of the experience of these multiple-function agencies could augment our

knowledge of the coordinating functions of the visiting nurse in home care; and of the scope, volume, and costs of services.

Homemaker services: Data on the need for homemaker service in a given home care program and on the effectiveness of such existing arrangements can add greatly to our knowledge of its role in comprehensive medical care. Delineation of those needs will also be a guide for establishing the functions of the homemaker with respect to simple nursing, domestic service, and care of children. Questions regarding frequency, volume, and duration of service, costs, and methods of financing can be answered by analysis of records of the homemaker service for various disease categories, types of household, and types of patients. Comparisons of what happens to patients and their families under similar conditions with and without homemaker service will yield needed data.

Data given in Table 22 of the *Source Book*[16] indicate that, in 1953, 50 agencies (8 public and 42 private) in 22 states were providing homemaker services to the chronically ill. The services performed include cleaning, cooking, marketing, laundry, mending, care of children, and in many instances personal care of bed patients. Fourteen of the reporting agencies provided for homemakers who would live with the family. The majority[39] usually arrange for full-time service five or six days a week. As with visiting nurse services cited earlier, cardiovascular disorders represented the major causes of disability for one-third of the patients served in the month of study.

Fitzsimmons[33] said that skilled case-work services should always accompany homemaker service to give guidance to the homemaker and assistance to the members of the family as needed.

Social case-work services: To a large extent, industrialization, urbanization, and mechanization of many of the service industries (including medical care) have created the need for medical social work to compensate for the lack of intimate knowledge of the patient, his family, and his neighborhood resources which characterized the family doctor of past generations.

This view was amplified by Cockerill.[25] She quoted Abraham Flexner (1915), who considered social work "not so much a definite field as an aspect of work in many fields," and suggested that social work is an endeavor to supplement certain existing professions, pending their future development. To him, the social worker served as a means of "controlling the keyboard that summons, cooperates with, and coordinates various professional specialists."

Cockerill, developing this theme, said that as a member of the health professions team, the medical social worker has characteristically identified the problems created for the individual or group when coordination and integration are lacking and has tried to help individuals and groups handle problems arising from uncoordinated services. She stressed that the social work practitioner on the health team should undertake responsibilities inherent in the collaborative, interdisciplinary process.

Studies of the appropriate functions of the social worker, her interrelationships with other members of the health team, and the results of her services can provide factual answers to many questions that arise in home care programs. Among expected results are a sound basis for deciding whether case-work services should be organized and administered for the family, for special chronic diseases, for children, or for the aged. Such studies can also reveal the advantages and limitations of services radiating from a health department, a welfare department, a hospital, a voluntary agency, or a combination of several such agencies; and

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can deal with required personnel and costs in relation to patients, families, physicians, nurses, hospitals, and the community.

Rehabilitation: This is also a relatively new and expanding field. We must extend knowledge concerning the feasibility, goals, and achievements of including physical and occupational therapy in a home care program. We need to know more about the conditions and age groups for which full rehabilitation to normal self-support is possible and the lesser aims that are rational for a cardiac housewife, an amputee, a hemiplegic, or a retired arthritic.

Little information is available on specific experience in rehabilitating patients in home care programs, although much that is written on rehabilitation goals and achievements in hospitals and clinics would seem to be equally applicable to home care, particularly with respect to increasing the capacity of the patient to perform unaided most of the essential activities of daily life.

Thus Cosin[26] wrote that good nursing and medical care plus rehabilitation reduced to a minimum the number of aged patients in Orsett Lodge Hospital in England who were physically disabled, permanently bedfast, and in need of every care and attention. In a two-year period, he said, 45 per cent of the patients over age 60 were improved and only 10 per cent remained bedfast.

Rusk[52] described a rehabilitation program in a veterans' hospital in Minneapolis which achieved dramatic results with 130 patients suffering from chronic neurological disease, many of whom had been bedfast for ten years. After nine months of physical medicine rehabilitation, 25 of the patients had left the hospital and were employed; 40 others had been discharged to their homes, capable of light work; 30 were ambulatory and undergoing advanced treatment; 25 were capable of some self-care; only 10 showed no improvement.

Covalt[27] cited similar activities in Rocky Hill, Connecticut, where 290 chronic patients needed functional training. Of the 207 for whom a full course of training was undertaken, all showed improvement, and the majority became able to walk, climb stairs, and travel.

Describing the rehabilitation service at Goldwater Memorial Hospital in New York City, Dacso[29] pointed out that provisions are made for home care to assist discharged patients to maintain and improve their physical gains. The results of the service in the hospital were as follows: of 167 patients, 91 were discharged, although before rehabilitation most of these patients had been hospitalized more than three years, and some for ten years or more. Patients not discharged were returned to their wards with physical ability so greatly improved that they required 50 per cent less nursing than before.

Special investigations might be designed to show whether special criteria govern the suitability of home and family if rehabilitation is to be possible. Information might be provided to determine how soon rehabilitation in various illnesses should be started and how soon outpatient services in a hospital or clinic should be substituted for home services. Analysis of experience can reveal, moreover, the frequency, volume, and duration of visits found necessary; the costs and by whom they are paid; the comparative effects on relatively similar patients with and without rehabilitative home services; the effects on the family and on the community in terms of earning power, family structure, productive activity, and welfare costs.

Schwartz,[54] in a recent Public Health Monograph reviewing the literature on rehabilitation of mental hospital patients, illustrated the need for definitions of goals, analysis of methods of approach, and appraisal of results for one type of long-term illness. A similar clarification of these factors is needed for other

conditions. Establishing indexes of the functions and results of rehabilitation will go far toward professional and public understanding and willingness to finance rehabilitative efforts and will demonstrate the real place of rehabilitation in a total health program.

Evaluation of Results.—Organized services to the patient in his home have been advocated on at least six grounds, as indicated in the following reports of experience:

1. *Advantages to the patient*: Experience at St. Heliers Hospital in Surrey, England,[48] indicates that home care promotes the happiness of aged patients and their families and permits the patients to participate in community life. In England, also, home care for the tuberculous[57] has been described as fostering incentives toward recovery and avoiding the dependency, hypochondriasis, family tension, and fear of resuming work that are often associated with long stays in an institution.

2. *Release of hospital beds*: The home care program at Harlem Hospital and other municipal hospitals in New York City has been cited[37] as an important factor in reducing ward occupancy rates. In England, according to Brooke and Wetenhall,[18] use of the patient's bed in his own home is dictated by the shortage of hospital beds and nurses.

3. *Reduction in delays in admission to hospital*: Trimble and his associates[58] cited the fact that six to eight months usually elapsed before tuberculous patients could be admitted to the county hospitals in Alameda County, California. A home care program for the tuberculous has cut the waiting time to no more than ten days for eligible patients.

4. *Economy*: The home care program of Montefiore Hospital in New York City (1949) costs the hospital about $3.00 per patient day as compared with an average hospital cost of $12.00 to $15.00 per patient day.[22] Annual reports of the hospital[41,42] cite the use of the program for cancer patients with support from the New York City Cancer Committee and for children with rheumatic heart disease with funds received from the New York Heart Association. These cost figures, however, do not include such expenses as food and laundry that are borne by the patient and his family—costs included in patient-day hospital costs.

5. *Education for the health professions*: Bakst[6] has described the home care program of the Boston University School of Medicine as giving medical students an opportunity to see patients in relation to their social, familial, and other surroundings and as a means of considering psychologic and emotional factors associated with illness. Abramson[2] recounted the Bellevue Hospital program in New York in the training program for student nurses. Student social workers get orientation in family problems of illness by similar techniques.

6. *Extending the resources of private practitioners*: Bluestone[13] pointed out the value of a home care program in giving physicians the advantages of a hospital's diagnostic and therapeutic resources even for nonhospitalized patients.

Careful analysis of achievements in light of specific objectives is required to test the results of a home care program. If benefits to the patient are the prime goals, research should be designed to determine the progress of mental, or cardiac, or tuberculous patients toward recovery under home care as compared with patients of similar age, income, family composition, and diagnosis receiving institutional treatment, and to obtain information on what happens to these patients and to their families during treatment and after discharge.

If economical use of available institutional facilities and funds is the main objective, research should reveal the effect of home care on the duration of hospital stay for specific conditions and age groups. Research is also needed to disclose the expense for such items as special diets and extra laundry incurred while the patient is at home and the effect of shifting various elements of the costs from

the hospital to the family or to other agencies of the community. Hospitals and other agencies will also need to determine, through their operating experience, whether patients should be evaluated for home care before admission, after some specific duration of stay, or only when it is clear that they are becoming "long-term" cases.

Whether benefits to the patient, economy, or some other consideration are the objective of home care programs, there is a paucity of information for an evaluation of the extent to which objectives are met by the several programs cited.

A first example of such evaluation is furnished by the three-year demonstration and research program of home care initiated in 1953 at the Montefiore Hospital in Pittsburgh. From the beginning, plans were made to establish an appropriate "control" group which would provide a basis for comparing the group receiving care. "Test" and "control" patients were selected at random from among persons considered eligible for home care from the standpoint of diseases, therapeutic requirements, and home conditions. A detailed cost accounting system was installed to measure the cost of recurrent hospitalizations of both "test" and "control" patients and, in particular, to determine other elements of cost to the patient, to the institution, and to the community as a result of home care services. A summary report of the first year of operation of this program appears in the *Chronic Illness News Letter*.[50]

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THE PATIENT IN AN INSTITUTION

Since for certain conditions or for certain phases of illness many patients must have care in an institution, data are needed on types of institutions and the kinds and amount of services required. Such data can provide a sound basis for planning construction programs. With the increasing proportion of the population aged 65 or over, it is well to assess the number of beds needed in mental institutions, in homes for the aged, in nursing homes, and in general hospitals.

Bluestone, in setting up his "Agenda for a Critical Exploration of Current Problems in Medical Care,"[12] has raised a series of questions which need answers as a basis for hospital policy. His statements will be drawn on extensively here, without quotation marks, for they indicate the important part research can play in planning, policy formulation, and administration of institutional facilities.

First, Bluestone stressed the need for definitions. What is meant by acute, chronic, convalescent, custodial, aged, hospital, home, curable, incurable, he asked. When should a patient be categorized "custodial"? At what point, if any, during the course of an illness is an institution justified in transferring a patient to less capable (or less resourceful) hands? It is easy to see how hospital policy can be revised and formulated on a more equitable basis when such questions are answered correctly and in absolute terms in relation to each other.

Bluestone's "Agenda" also cited the need for a well-reasoned critique of the older and still prevailing methods of dealing with prolonged illness in homes, hospitals, and elsewhere. In other words, we need to know the what, where, how, how much, and why of existing services as a basis for dissatisfaction with what we have and as a source of experience for the substitutes that may be adopted. He went on to say that the criteria for admission to hospitals and other institutions like homes for the aged and for transfer from one type of institution to another or to the patient's home will have to be redefined and restated in the light of the deep-seated changes which have occurred in medicine.

In the remainder of this section examples of experience and the questions they raise are noted for only two subjects: (1) types of institutions and their functions and (2) rehabilitation in the institutional setting.

Types of Institutions and Their Functions.—The place of the general hospital in the hierarchy of institutions for the sick and disabled has been analyzed more extensively in Great Britain than in this country, perhaps because the transfer of so-called "poor law" institutions to the regional hospital system of the National Health Service and the war-induced shortages of facilities and personnel required a thorough investigation of the functions of various types of institutions.

General hospitals: By and large, general hospitals are designed and equipped for short-stay patients whose acute conditions need extensive laboratory and other diagnostic equipment, surgical intervention, continuous skilled nursing, or prompt recourse to the services of physicians and medical specialists. The modern hospital was thus developed and equipped in a period when the age distribution of the population and the prevalence of acute conditions warranted less attention to long-term illness than is now necessary.

Studies in Great Britain by McKeown and Lowe[10] and Amulree[3] have indicated the current role of the general hospital, the types of patients it actually serves, and for how long. The purpose of the investigations has been to determine how many hospital patients could be cared for equally well elsewhere and more economically in terms of patient-day costs and use of highly trained personnel.

Many of these studies have been mainly concerned with the aged in hospitals and former poor-law institutions. Amulree and his associates[3] found, for example, that the average length of stay in the University College Hospital in London was 40.2 days for elderly patients as compared with 35.1 days for other adult medical patients. They also found that quick turnover of elderly hospital patients may be achieved by careful screening before admission, treatment in outpatient departments for those who do not need hospitalization, ward care that emphasizes keeping patients ambulatory, and prompt discharge to a home care program or long-stay annex as soon as the patient's condition permits.[4]

The British Medical Association, in its recommendations on the use of the right bed for the right patient,[16] cited the experience of a general hospital with 8 elderly men patients who did not need active treatment. The beds these patients occupied could otherwise have been used for 360 acute surgical cases. Another institution had 714 elderly chronic invalids, more than two-thirds of whom were bedfast when it was taken over for use as a general hospital. By thorough diagnosis and active treatment, the hospital was able to rehabilitate and discharge many of the bedridden patients and reduce the number of beds for elderly chronic patients to 200.

Bluestone[14] envisioned the hospital of the future as a central unit housing all diagnostic and therapeutic facilities and an adequate number of "acute" beds. Radiating from this central structure and varying in location, he saw subsidiary units, including (1) department for chronic care, (2) private and semiprivate sections, (3) outpatient department, (4) tuberculosis department, (5) neuropsychiatric division, (6) group practice and home care unit, (7) doctors' office building, (8) rehabilitation center, (9) convalescent unit, (10) health center, all using the facilities of the central structure. The British Medical Association's recommendations for care of the elderly and infirm,[16,17] centered in a "geriatric" department of the hospital, include supplementary suggestions for additional affiliated units: (1) short-stay hostels for patients undergoing investigation and not needing expert nursing, (2) convalescent hospitals for patients insufficiently recovered to return home, and (3) transportation facilities for nonbedridden patients to convey them between their homes and outpatient departments.

These data and viewpoints suggest the need for more precise information on:

1. The extent to which the hospital and its affiliates can form a diagnostic center and "therapeutic community" for patients with long-term disabling illness (to use a term employed by Jones[36]).

2. The extent to which the general hospital best serves mainly as a clearing house for diagnosis and emergency treatment, transferring patients as soon as possible to special units for prolonged care and rehabilitation, for relatively short-term convalescence, or for terminal care in hopeless cases.

3. The effect on patients, hospital personnel, medical and nursing education, and hospital finance produced by segregation versus nonsegregation of these types of patients.

4. The frequency and the conditions with which convalescent, long-term, and other patients need readmission to the general hospital from home care programs and from special institutions.

Chronic hospitals or wings: Aside from information already touched upon, there are no data on the advantages and limitations of providing separate hospitals or special wings for chronic patients. We lack information, for example, on the frequency and conditions with which patients in these facilities need the personnel and equipment of the general hospital; the special personnel qualifications and orientations desirable for the care of long-term patients; and the arrangements required for continuity of care when the patient is moved from the general hospital to the special facility.

Hostels, halfway houses, and long-stay annexes: British experience with hostels, halfway houses, and long-stay annexes has considerable significance for community planning, since it has been developed in a country faced with shortages of personnel, funds, and materials for constructing facilities and with large and growing demand for institutional care of the aged and the chronically ill.

The British halfway house, according to Ellicott,[30] is a hospital annex caring for frail ambulant patients who are considered to be at a halfway stage between hospital and home. The average bed capacity is 35 and the average stay is six weeks. Since the patients take care of most of their own needs, the cost of operation is from 30 to 60 per cent less than that in a "geriatric" unit of the hospital. The long-stay annex, on the other hand, receives the permanently bedfast patient who is considered incapable of further rehabilitation. It is usually a small unit with day and night nursing service, which attempts to provide a homelike atmosphere, recreational activity, and a daily period out of bed, if possible. The patients of both annexes are the responsibility of the hospital.

The investigation by McKeown and Lowe[40] of patients in a British hospital region gives data on the classification of patients, the appropriate type of arrangements for their care, the number in each classification group per million population, and the costs per patient-week, as follows:

Group 1, requiring frequent medical attention or skilled nursing, should be cared for in "geriatric" wards of general hospitals; they would represent 300 patients per million population and the cost of care would be £10-15 per patient per week. (In April 1953, the average weekly earnings in manufacturing and selected industries in the United Kingdom was approximately £8.)

Group 2, patients confined to bed but requiring for the most part only simple nursing and infrequent medical attention, should be cared for in long-stay annexes; they would represent 600 patients per million population and the cost would be £5-7 per patient-week.

Group 3, frail ambulant patients requiring a little nursing care and occasional medical supervision, should be in nursing homes attached to old people's homes; they would represent 300 patients per million population and the cost would be £4-5 per patient-week.

Group 4, ambulant old persons not in need of medical or nursing care, should be in old people's homes; they would constitute 1,000 per million population and the cost per patient-week would be £2½-3.

Similar studies of patients in veterans' hospitals in the United States and in institutions for the tuberculous or the mentally disordered could reveal the potentialities for use of simpler, less expensive annexes affiliated with general or allied special hospitals in the treatment of long-term conditions, and the equipment, personnel, and funds needed for such annexes.

Nursing homes and convalescent homes: Important data are being collected on the characteristics of nursing home patients.

A study of patients in the registered nursing homes for adults in Maryland (reference 46, Tables 45-47, and reference 51) revealed that the median age was 78 years; 12 per cent were completely bedridden; 60 per cent were mentally confused part or most of the time; only 77 per cent were fully continent. About 28 per cent had primary diagnoses of heart and circulatory diseases, and only 40 per cent had been in the homes for less than one year. Only 12 per cent received no nursing services, and 25 per cent received no assistance in personal care.

Comparable studies being conducted in several states on nursing and convalescent homes will turn additional light on their functions. Such data will be needed in defining the roles of such homes, in planning sound expansion of these facilities, and in assuring that they meet acceptable standards of medical supervision and licensure. Among factors to be considered in such studies for both types of homes are: personnel or arrangements for medical and nursing services and rehabilitation; the extent to which the homes include persons who are in institutions solely because they lack suitable homes and families; the condition of patients on discharge; the need for separate facilities for the aged or for the mentally deteriorated; the costs of care in these homes compared with those of other types of institutions; the control needed over the quality of care and facilities; the effect of stay on patients and their families; and the potentialities and techniques for the development of a therapeutic outlook and realistic goals for rehabilitation.

Custodial care: Bluestone[12] has said that the time has come to restate criteria for admission to homes for the aged and to other custodial establishments. Such institutions, he pointed out, are substitutes for the patient's home and never for the hospital. Nevertheless, they must at times meet medical emergencies.

Research can provide the facts to determine the most desirable arrangements for establishing a complete "therapeutic community," and for determining the interrelationships among all institutions of the community. It will help to determine the best relationships among allied facilities in order to prevent duplication and assure effective use of existing and future resources.

Rehabilitation in an Institutional Setting.—Rusk[39] said that hospitals complain that the chronically ill are responsible for their overcrowding but do little to provide the retraining services that will permit many patients to leave. He further cited a New York State survey in which the great majority of the hospitals frankly stated that they tried to avoid admitting patients with long-term illness.

Rehabilitation, Rusk continued, begins with the belief that the doctor's responsibility does not end when an acute illness is over or surgery is completed, but must go on until the patient is trained to live and work with "what he has left." Rehabilitation is thus an integral part of medical care and becomes increasingly important with advances in life expectancy.

Several examples of experience in successful rehabilitation have been noted earlier in the section on the patient at home. Others can be added. Thus, the Liberty Mutual Insurance Company[10] described the results of a seven-month rehabilitation program for a man who had lost both arms a few inches below the elbow. He learned to put on his arms, dress, shave, feed himself, light a cigarette, make change, open doors, drive a car, and use tools, and was able to resume his former job at the same rate of pay. The cost of hospital and surgical treatment was estimated as $3,336; under the Missouri workmen's compensation law he will receive a disability pension that will probably total $20,000 even though he has returned to work. The rehabilitation cost, at an estimated total of $2,641, however, has not only benefited the man by returning him to a normal life and occupation, but has made it unnecessary to provide him the care of an attendant at an estimated total cost of $30,800. At the Boston Rehabilitation Center, 2,325 injured persons have been treated, and of those who have completed treatment 67 per cent have returned to work. In cases of paraplegia without rehabilitation, some injured workers remain in the hospital for life with workmen's compensation, medical, hospital, and nursing costs running as high as $1,000 a month and ultimate costs to the insurance company that in some cases can exceed $250,000.

Operation of a demonstration rehabilitation program in the General Hospital in Washington, D. C.,[19] is reported as having reduced the average annual days of hospital stay for orthopedic patients from fifty-five to thirty-three and for approximately 500 patients has saved taxpayers about $147,000 in a single year. Among the patients with cerebral vascular accidents, 90 per cent have been enabled to go home ambulatory and capable of self-care whereas after the same period of hospitalization without rehabilitation, such patients had formerly been sent home bedridden and helpless.

Ferderber[32] has described the results of a five-year rehabilitation program in two public institutions for the indigent in Allegheny County, Pennsylvania. Among 101 patients with fractures of the lower extremities, 60 per cent were discharged after rehabilitation and 25 per cent ultimately returned to work. Of 196 hemiplegics, 38 per cent could be discharged and an additional 44 per cent were definitely improved. Most of the women in the infirmary for long-term patients were incontinent, bedfast, apathetic, and physically and mentally deteriorated. As a result of the rehabilitation program, incontinence has virtually disappeared, some patients have been discharged to their homes, and others have become ambulatory. One important element in this success is ascribed to the sympathetic interest shown by the staff in the individual patient, reflecting the importance of psychologic factors in the behavior of these patients.

"Operation Knoxville"[56] was planned to meet the triple problems of labor shortage, need to cut city expenditure, and heavy welfare costs resulting from disability of the family wage earner. A vocational rehabilitation program started in 1951 resulted in the rehabilitation and re-employment of 100 handicapped persons as a start toward the goal of cutting expenditures for aid to dependent children by $175,000 a year through rehabilitation of the wage earners in at least one-half the 500 families on the public assistance rolls.

The experiences cited can be developed to yield helpful information for other communities on many questions that need answers, such as the appropriate timing, sequence, and administrative arrangements for physical therapy, occupational therapy, vocational training, counselling and placement services, sheltered employment, and follow-up after discharge from treatment; the importance of psychologic factors; conditions that do not respond to rehabilitation; the length of time various groups of patients need to remain in a protected environment; the aims and results of rehabilitation for specific conditions in terms of capacity for self-care, freeing other family members for gainful employment,

and actual earnings and work histories of rehabilitated persons compared with the estimated cost of neglect.

Recent analyses of rehabilitation of psychiatric patients could well be paralleled for cardiac cases, hemiplegia, various orthopedic conditions, cerebral palsy, and the like. Attention is called to two articles on psychiatric rehabilitation by Williams[64,65]; to the review of the literature by Schwartz[54]; and to *The Therapeutic Community*, by Jones.[36] These publications show for the field of mental illness the types of problems and evaluations of results that suggest fields of experimentation and research in rehabilitation programs for other conditions.

Organizational problems such as those related to the location and use of physical and occupational therapy equipment, personnel, and techniques in general hospitals, rehabilitation centers, and other institutions and their interrelationships can be answered best by carefully designed research. Such research can also give answers, for example, to such questions as: Should rehabilitation of cardiac cases be a separate program or should it be integrated with programs for such other conditions as tuberculosis, poliomyelitis, blindness?

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INTEGRATION OF SERVICES AND FACILITIES

Many aspects of integration of services and facilities have been cited in the foregoing sections on the Patient at Home and the Patient in an Institution. This section therefore will be limited to a brief review of three topics: (1) integration of preventive and therapeutic efforts; (2) regional programs for the extension of the resources of a medical center to wider areas; and (3) counselling and referral services.

Integration of Preventive and Therapeutic Efforts.—Multiple screening for chronic illness illustrates an integrated technique for the discovery of the suspicion of latent illness among people who are unaware of incipient disorders, as well as for the identification of known conditions that need to be brought under treatment. Community resources that have been pooled for mass screening tests include industry,[8] private practitioners,[45] voluntary health agencies,[11] public health departments,[11] hospitals,[53] labor groups,[63] and civic groups.[11]

Considerable study is still needed on technical improvement to increase the specificity of the several tests, to develop additional simpler tests, to broaden the base of the population screened, and to reduce the costs. Still more work is required to provide effective methods of follow-up for accurate diagnosis and treatments, using all available community resources to forestall the development of long-term disability and to make the benefits of modern medicine accessible to persons with chronic illness, especially those in an incipient stage. Long-term studies of families, such as those initiated in the Eastern Health District of Baltimore, Hagerstown, and the Arsenal Health District of Pittsburgh, supplemented by control studies of groups receiving comprehensive treatment, can reveal the extent to which integrated community efforts can set patterns for optimal organizational and financial arrangements for community action.

Wishik,[66] in outlining an administrative guide for a community cerebral palsy program, has pointed out many problems of classification of the disorder; integration of case-finding, diagnostic facilities, and treatment resources; and choice of realistic goals for rehabilitation for different types of conditions.

Comparable administrative guides for a wide range of diseases requiring long-term care could be derived from similar analysis of experience concerning what a community might and can do for other chronic conditions separately or in combination.

Regional Programs for the Extension of Medical Resources.—Obviously not all communities need or could support the comprehensive diagnostic, therapeutic, and rehabilitative skills and facilities available in large medical centers. One solution to the problem of equalizing the distribution of present resources for medical care is the regional setup in which a teaching hospital, sometimes directly affiliated with a medical school and sometimes without that affiliation, extends its services to smaller hospitals within a designated area, and these smaller hospitals, in turn, form centers for the provision of services to still smaller units.

Existing regional programs in the United States are primarily educational, designed to relieve the plight of the rural physician resulting from his isolation from the rapid developments in medical knowledge. A recent unpublished study conducted by the Public Health Service in cooperation with the American Public Health Association reveals the organization, objectives, and services provided in several regional programs, most of which have been established by medical schools with the aid of funds from philanthropic organizations.

This study will provide an analysis of experience in this type of integration of facilities and will indicate the administrative problems that need additional research for solution. Other forms of research, moreover, can set base lines for community planning by investigating where residents of various areas go to get medical, dental, hospital, and related services, the frequency of the contacts with health resources outside the community, and the distance traveled. One such study[24] delineated existing self-sufficient, mutually interdependent, and deficient health service areas with respect to various types of health personnel and resources.

Moreover, control studies designed to measure the effect on physicians and patients resulting from the provision of consultative and advisory services from a medical center to the physicians and hospitals of outlying areas are needed, especially with respect to long-term care in disabling illness. Studies of the effect on hospital costs, staffing, and quality of care can also reveal the results of joint purchase, budget and cost accounting aids, records and reporting standards, rotating internships and residencies, and the like.

Counselling and Referral Services.—Central counselling and referral services for the chronically ill have been established under various auspices: for example, by the Institute of Medicine in Chicago[20]; by the Health and Welfare Council of Philadelphia[61]; by the Council of Social Agencies in Newark, New Jersey[21]; by the Community Chest of San Francisco[23]; and by an independent agency in Milwaukee.[43] The functions of these counselling and referral agencies vary also, including one or more of the following services: collection and dissemination of information on facilities and needs; help in arranging for care of individual patients; promotion of plans for providing facilities and services; sponsorship of legislation; and cooperation with professional and civic groups.

Experience in these services might well be studied in relation to their scope, costs, and results. For example, one can determine whether the program should

be for specific age groups, for low-income groups, for specific diseases, for long-term care alone, or part of an integrated plan for all health needs and resources of a community. Other investigations can be designed to show how costs are met and the effect of the program in reducing delays in receipt of care, in utilizing community resources to the best advantage, and in formulating programs for construction of facilities.

CONCLUSIONS

The examples of existing experience in caring for long-term patients, here cited, and the notation of problems still unsolved are, of course, illustrative only. They serve, however, to underscore a few broad conclusions:

(1) Programs vary widely in scope, objectives, costs, administrative arrangements, and results.

(2) They represent a variety of limited efforts to solve some of the numerous and complex problems associated with long-term illness.

(3) Each program is essentially an experiment or demonstration project which can set patterns for more effective and more comprehensive measures for long-term care of the chronically disabled.

Profit from these experiments can be derived, however, only if those who administer the programs fully understand the objectives and results of their efforts in terms of costs, case loads, personnel requirements, and impact on the patient, his family, and the community as a whole. In many instances, program administrators fail to realize the importance of careful evaluation of their experience as a guide to their own future operations and to the work of others.

All program administrators therefore should do their own research, building into their program provisions for adequate records and reports and for periodic studies that will measure quantitatively and qualitatively what has been done, for whom, how effectively, at what cost, and with what resources. Careful analysis of even limited experience will thus help to build our body of knowledge concerning, say, a specific type of service to a specific age group for designated disease conditions. Persons responsible for similar or comparable programs in the same or different communities can use these analyses as a basis for establishing new programs or for improving those already in operation. What is more, persons concerned with broader problems of health and welfare, by piecing together the factual data derived from a variety of experience, will have practical guides for planning programs of wider scope and objectives.

Long-term illness, however, is associated with so many biologic, economic, and sociologic factors that many of its variables transcend the scope of analysis possible in any single program or demonstration project. To discover some of the common denominators which may underlie variations in race, income, and educational level, utilization of preventive and therapeutic procedures, housing, or occupation, for example, illness experience needs to be studied through large-scale, uniform, nationwide, or communitywide surveys. Such surveys require adequate numbers of people in the groups examined, elaborate and carefully designed study methods, and appropriate means of controlling the number and

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range of variables. For various parts of such surveys, however, the experience, records, and participation of the program administrator are indispensable adjuncts.

The unknowns in the field of chronic illness are a challenge to man's powers of observation, analysis, and deduction of inferences and relationships.

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A REVIEW OF ILLNESS FROM CHRONIC DISEASE AND ITS VARIATION WITH AGE, SEX, AND SEASON, WITH SOME TRENDS

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INTRODUCTION

ALTHOUGH the death rate from all causes in the United States has been decreasing for many years, the mortality from some of the most important chronic killers has continued to rise. Among the latter are heart diseases, particularly the arteriosclerotic type, malignant neoplasm, and even a few diseases such as diabetes mellitus for which good control methods are available.

On the other hand, some of the less frequent chronic and related diseases are largely or partially under control by prevention or the use of antibiotics and other drugs to avoid serious outcome such as permanent impairment or death. But in general the noninfectious chronic diseases have yielded more slowly to control measures than the many infectious diseases such as tuberculosis, syphilis, the common diseases of childhood, pneumonia, typhoid, typhus, and others.

The important development of antibiotics and new drugs, and the marked improvement in the general level of living in the past half century, have accelerated the downward trend of the death rates from both acute and chronic infections and some other diseases, but have not yet succeeded in suppressing the great noninfectious chronic degenerative diseases. However, sufficient progress has been made in the control of many serious chronic diseases to change the attitude of researchers from despair to hope.[1] ACTH and cortisone have been useful in rheumatoid arthritis and a considerable number of other diseases. Here, as in other newly developed drugs, there have been minor and sometimes serious side effects in the early use of the new therapeutic agents. A great many other developments in the various "wonder drugs" have taken place; the intention here is merely to indicate that their application to the infectious diseases has thus far been more successful than in the field of the noninfectious diseases.

CHARACTERISTICS OF THE TOTAL CASE LOAD OF CHRONIC AND ACUTE ILLNESS

In the study of almost any type of data that may be undertaken, there are few persons so familiar with the subject that they can assess the magnitude,

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important characteristics, or other important statistical aspects of the problem without some related data for comparative or control purposes as a measuring rod to apply to the data under primary consideration.

In a study of the extent of chronic illness in the population and the characteristics of the chronic patients, some comparison with acute illness seems to be a necessary and logical step. In this study, comparisons of chronic and acute illness of various kinds will be made from data by diagnosis, age, sex, and severity of the case, collected mainly in five periodic household canvasses. The five surveys covered more than 80,000 full-time person-years of observation.

In the matter of severity, the total illnesses are classified as: (a) nondisabling cases, including those which caused no loss of time from usual activities; (b) disabling cases, which refer to those which involved one or more days lost from work away from home or at home, including housekeeping, school, or other usual activities. Bed cases constitute a subgroup of disabling cases and include those patients confined to bed at home for one or more days or in a hospital for one or more nights, or both. Thus the total cases amount to the sum of the nondisabling and disabling; all bed cases include hospital cases, and all disabling cases include those patients in bed at home or in a hospital or both.

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These five surveys included 38,544 person-years of observation for a group of families in eighteen states who were observed one full twelve-month period; 4,236 person-years for families in eighteen states observed less than twelve months; Cattaraugus County, New York, with 10,142 person-years; Syracuse, New York, with 6,341 person-years; and the five-year Baltimore Eastern Health District illness study with 21,505 person-years of observation. The latter three surveys were somewhat more intensive with special reference to chronic disease; an inventory of all persons with any chronic disease (nondisabling or disabling) was made at the beginning of these studies, and other persons with chronic diseases, both new and those missed in the first inventory, were added as of the date of entrance into the study or as of the onset of the illness if it was a new case. Because of this more intensive effort to record all chronic cases, and because days of disability and days in bed were not available by age and sex for all five surveys, some of the data on chronic diseases will be confined to these three surveys.

The annual total case rate in the five surveys was 1,060 per 1,000 canvassed population or just over one illness per year per person. However, in the three most intensive surveys, the total annual case rate was 1,289 per 1,000 population, of which in 615 cases per 1,000, or 48 per cent of all recorded cases, the patient was disabled for one or more days; in 369 cases per 1,000 population, or 29 per cent of all cases, the patient was confined to bed for one or more days; and in 56 cases per 1,000 population, or 4.4 per cent of all cases, the patient was confined to a hospital for one night or longer.

Of the annual total of 1,289 recorded cases per 1,000 population in the three surveys, 170 per 1,000 population, or 13 per cent of all cases, were chronic, and the other 1,119 per 1,000 population, or 87 per cent of the total, were acute.*

*See Appendix B.

The proportions of all chronic and of all acute cases that were disabling were 57 and 46 per cent, respectively; of the chronic disabling cases, 66 per cent of patients were in bed for one or more days, as compared with 59 per cent of those with acute cases. Of the disabling days in chronic disabling cases, 35 per cent were spent in bed (at home or in a hospital), as compared with 33 per cent of days in acute cases. Of the patients with chronic disabling cases 18 per cent were hospitalized and spent 22 per cent of their days of disability in a hospital, as compared with 7.4 and 7.9 per cent, respectively, for acute cases. Finally, of the patients with chronic bed cases 28 per cent were hospitalized and spent 64 per cent of their bed days in a hospital, as compared with 13 and 24 per cent, respectively, for acute cases.

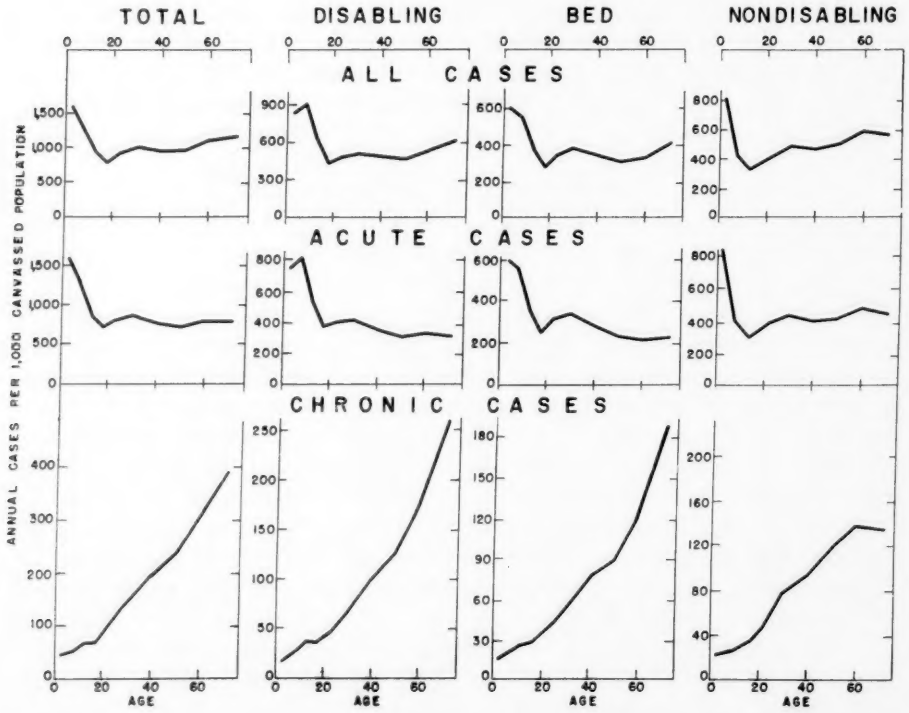

Fig. 1.—Annual age-specific case rates for all and for three severities of acute and chronic illness per 1,000 canvassed population—5 surveys with 80,768 full-time person-years of observation.

As a preliminary step in an examination of age distribution, it seems worth while to compute certain statistical measures or rates for the group of chronic diseases as a whole and to compute corresponding rates for the group of acute diseases. Fig. 1 is based on the five studies of illness.[2] It is seen in this figure that the case rates for the two broad types of illness vary with age in entirely different ways; acute disabling and bed cases have their highest rates in childhood but after a low point around 15 to 20 years, with a slight rise thereafter,

the acute case rates tend to decline or remain approximately constant from roughly 30 to 75 years of age.

In contrast, chronic case rates rise rapidly with age, particularly disabling and bed cases. Nondisabling chronic case rates do not rise as rapidly as those of the more severe types and actually cease to rise in the oldest ages, presumably because many nondisabling chronic cases in the earlier ages tend to become disabling in the older ages. The slower rise with age in nondisabling chronic cases in the older ages is reflected also in the total of all severities of chronic cases.

In the study of illness in the general population which was mentioned previously,[2] 103 rather specific diagnoses* emerged with enough cases for statistical analysis. Of these 103 diagnoses, thirty-three (32 per cent) were composed of cases the great majority of which were chronic in nature. The other seventy diagnoses (68 per cent) were predominantly acute.

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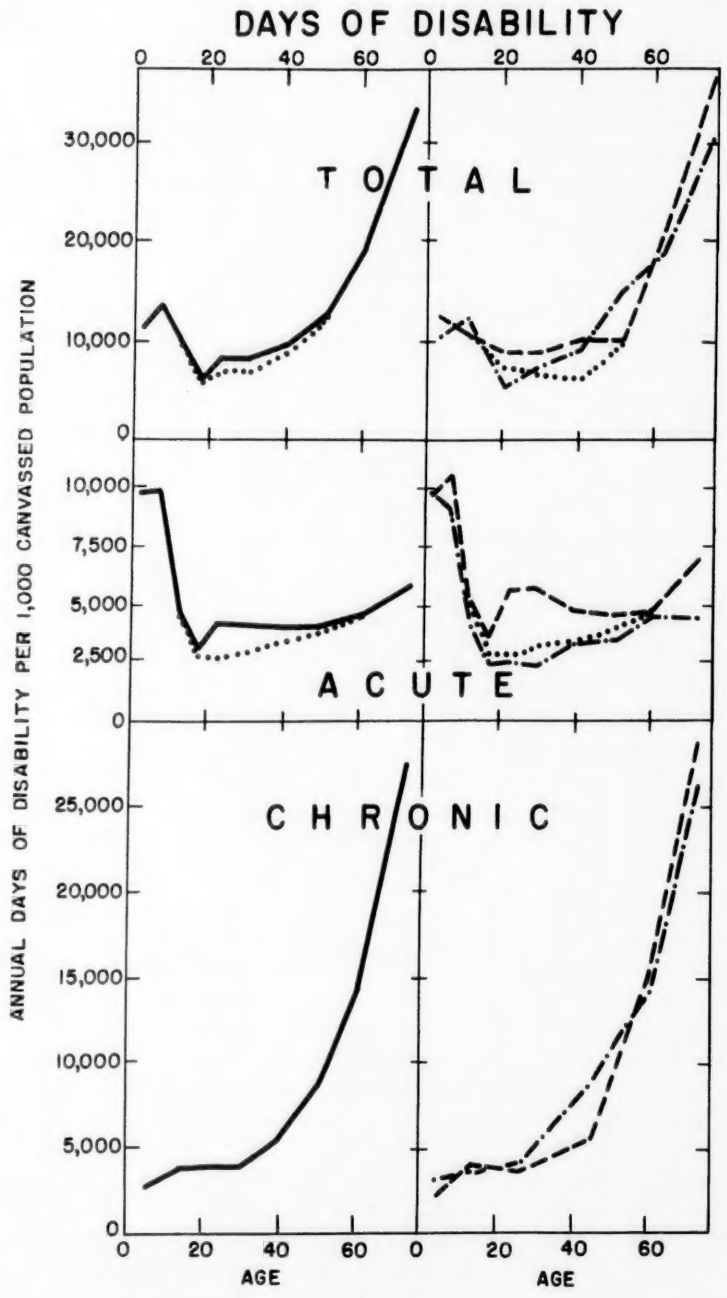
In the three surveys the total disabling days for chronic diseases amounted to 7,126 per 1,000 canvassed population, of which 2,459 or 35 per cent were bed days, and 1,562 per 1,000 population or 22 per cent of all chronic disabling days were hospital days. Comparative rates for acute diseases indicate that the total acute disabling days amounted to 5,166 per 1,000 population, of which 1,719 or 33 per cent were bed days, and 410 or 7.9 per cent were hospital days. Thus the ninety-seven chronic disabling cases per 1,000 canvassed population produced 38 per cent more disabling days than the 518 acute disabling cases; the 64 chronic bed cases per 1,000 canvassed population produced 43 per cent more bed days than the 305 acute bed cases; finally the eighteen chronic hospital cases per 1,000 population produced 281 per cent more hospital days than the thirty-eight acute hospital cases. To look at the matter from another viewpoint, the mean days of disability per acute case was 10.0, of bed was 5.6 days, and of hospital care 10.6 days, as compared with 73, 39, and 88 days, respectively, per chronic case.

Fig. 1 shows, for the five surveys, case rates by age for both sexes combined. Figs. 2 and 3 show, by sex and age, rates for days of disability and days in bed as well as cases for the same two categories, for the three surveys where special attention was given to complete recording of facts about chronic disease. Although the rates are higher, they are here plotted on scales to compare relative age curves rather than the absolute heights of the rates. Thus the curves for cases, both disabling and bed, are similar to those shown in Fig. 1. However, the total and the chronic days of disability (Fig. 2) both increase with age more rapidly than the case curves. Moreover, this rapid increase with age for days of disability is not so true of days in bed (Fig. 3), particularly for chronic cases. Presumably this difference reflects the medical practice of not ordering aged patients to bed for long periods if they are able to be up and about.

As to sex differences, the case rates, both acute and chronic, are usually higher for adult women than for men of the same ages, but the differences are

*See Appendix A.



A.

Fig. 2.—Annual disabling case rates and annual days of disability per 1,000 persons under observation, by age and sex—three surveys with 37,988 full-time person-years of observation (Baltimore, Md., Syracuse and Cattaraugus County, N. Y.). __ Both sexes. . __ . __ .__ Male. __ __ __ Female. ..... Female except genital and puerperal.

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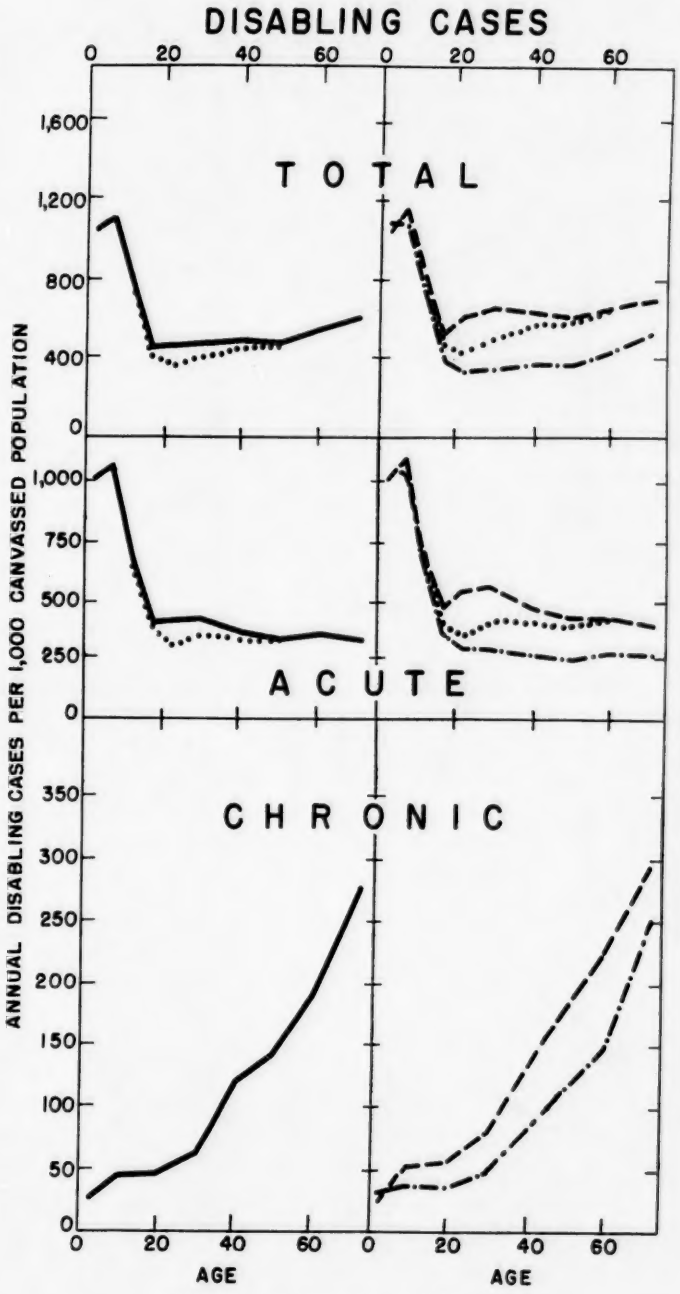
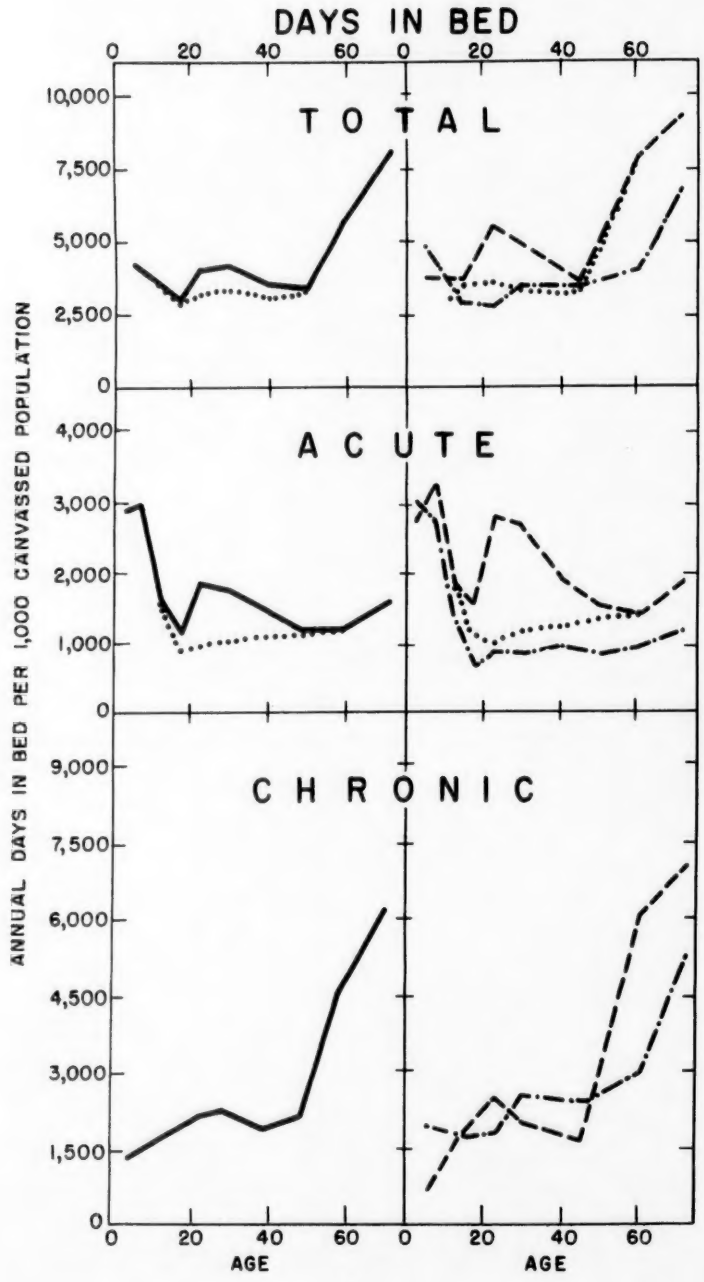


Fig. 2 B. *(For legend see opposite page.)*



A.

Fig. 3.—Annual bed case rates and annual days confined to bed per 1,000 persons under observation, by age and sex—three surveys with 37,988 full-time person-years of observation (Baltimore, Md., Syracuse and Cattaraugus County, N. Y.). ___ Both sexes. . — . — . — Male. — — — Female. ..... Female except genital and puerperal.

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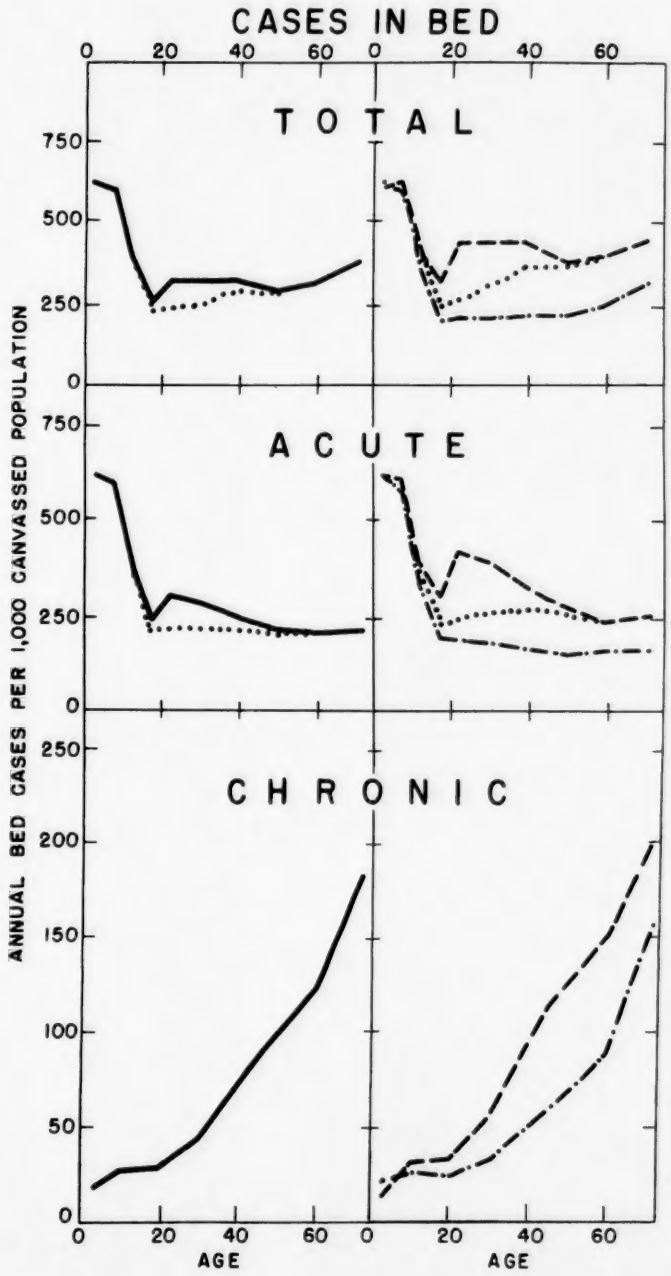

Fig. 3 *B.* *(For legend see opposite page.)*

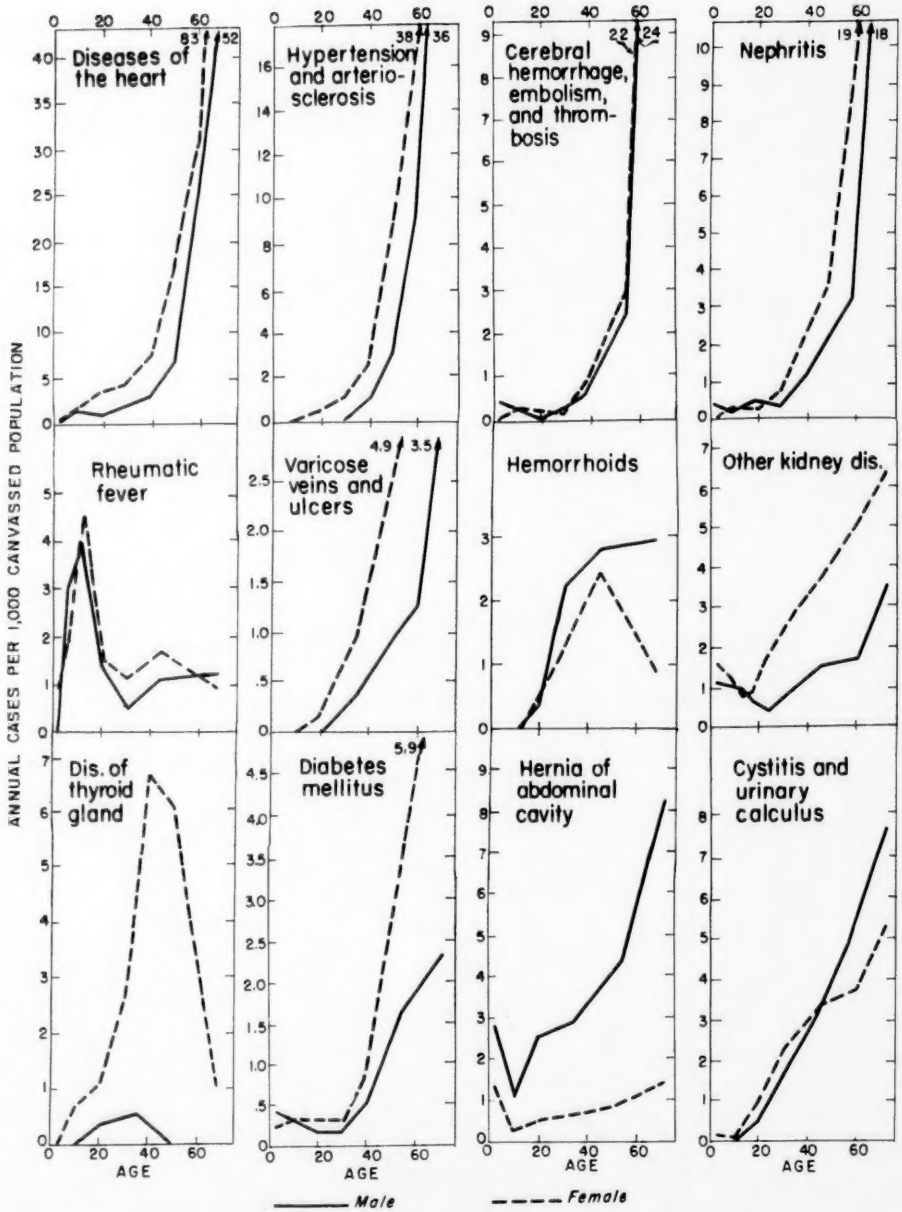

Fig. 4.—Annual age-specific bed case rates per 1,000 canvassed males and females for cardiovascular-renal and some other chronic diseases—five surveys with 80,768 full-time person-years of observation.

considerably less when the female genital and puerperal conditions are excluded. For the chronic cases the excesses in the rates for women are considerably greater in terms of cases than of days of disability or days in bed.

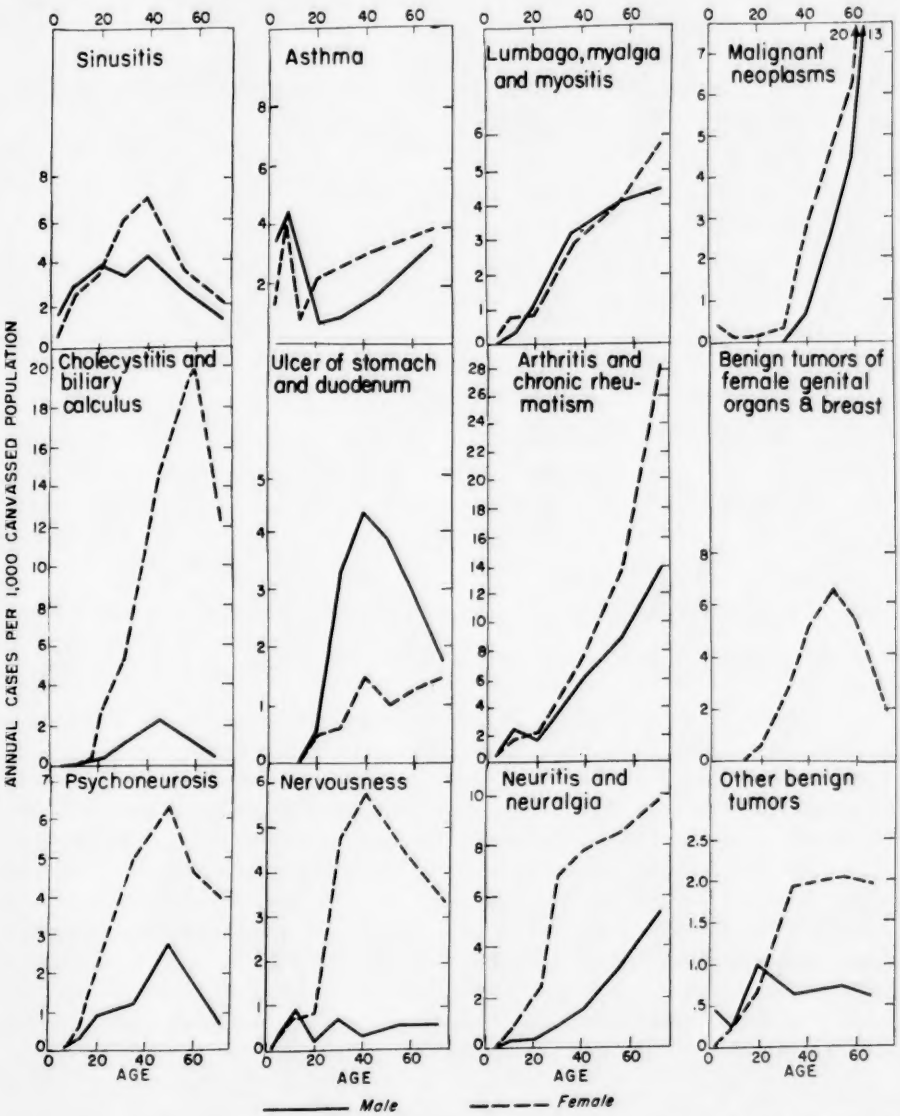

Fig. 5.—Annual age-specific bed case rates per 1,000 canvassed males and females for miscellaneous other chronic diseases—five surveys with 80,768 full-time person-years of observation.

AGE AND SEX VARIATION IN SPECIFIC CHRONIC DISEASES

In the preceding section I have discussed some important distinctions and comparisons between chronic and acute diseases as groups. But the physician

sees his cases as patients with specific diseases. Figs. 4 and 5 show by age and sex the chronic diseases as recorded in the five surveys. The data here used are cases confining the patient to bed for one or more days; as nurse and dietitian in general charge of the sickroom, the housewife probably remembers bed cases better than any other type.

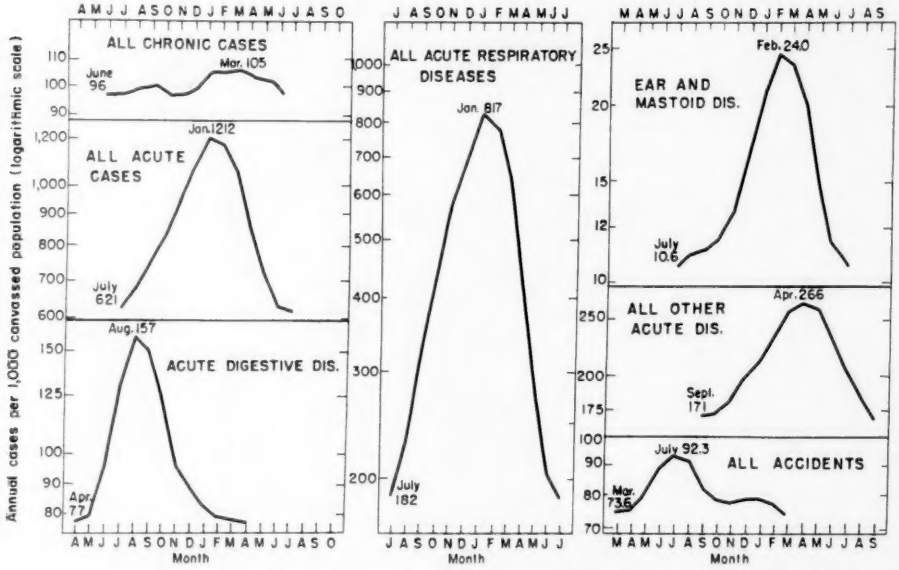

Fig. 6.—Relative seasonal variation in all chronic cases and in broad groups of acute cases.

In the majority of the chronic diseases with data available for this study, women have slightly but consistently higher rates than men. In the cardiovascular-renal group the only exceptions are cerebral hemorrhage, rheumatic fever, and hemorrhoids, the first two showing little consistent difference between the sexes. However, there are notable exceptions in that some diseases that may occur in either sex nevertheless occur predominantly among females, and a few others occur predominantly among males. For example, diseases of the thyroid gland, cholecystitis and biliary calculus, diabetes mellitus, neuritis, psychoneurosis, nervousness, arthritis, and benign tumors are exceptionally high among women. However, ulcer of the stomach and duodenum, hernia, and, among the acute conditions, accidental injuries and some other diseases are just as exceptionally high among men.[3]

SEASONAL VARIATION

In the course of a single year, relatively few new chronic cases occur in the sense of the acquisition of a chronic disease which the patient has never suffered previously. However, acute exacerbations or attacks of chronic diseases which existed prior to the beginning of a survey are more common. Many of the chronic diseases, particularly in the earlier stages of the cardiovascular-renal

group, are without disability except in terms of these attacks. Moreover, many of the chronic diseases are insidious in their onset so that the time of the original onset is often hard to determine. By the tabulation of the acute attacks of chronic diseases, one can get a rough idea of the season of the year in which the

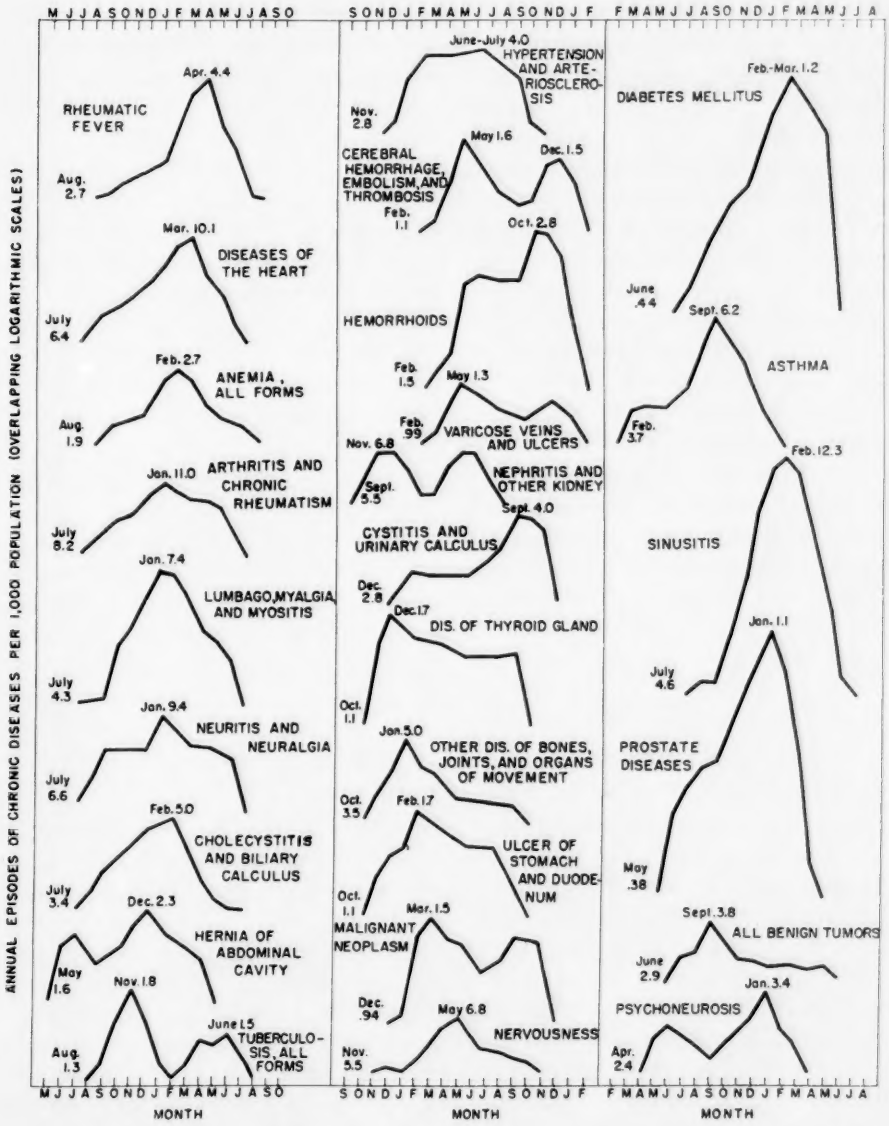

Fig. 7.—Relative seasonal variation in detailed chronic diagnoses. (Based on annual case rates for each month for periods in each survey of twelve consecutive months or multiples thereof. Data smoothed by three-period moving average with occasional combination of two adjacent months with apparently meaningless fluctuations.)

disease is likely to be more active and cause more trouble for the patient. Fig. 6 shows on a logarithmic vertical scale the seasonal curves of all chronic cases and of all acute cases, together with a few important groups of acute diseases. It is here seen that the seasonal variation in acute attacks of chronic diseases is very small as compared with the variation of all acute diseases, and particularly as compared with acute respiratory, digestive, and ear and mastoid diseases.

In Fig. 7 similar seasonal curves for specific chronic diseases are plotted on a much larger logarithmic scale. Thus the two charts are not comparable, but the various seasonal curves on each chart are comparable with other curves on the same chart.

Because of small numbers of cases, the data shown in Fig. 7 have been smoothed by a three-period moving average, with occasional combinations of two monthly values to avoid meaningless fluctuations. To save space no vertical scale numbers are used but the low and high seasonal values are entered on each curve in terms of annual rates for the month. Because this is a logarithmic vertical scale, the shape of a given curve is the same whether the actual rates be large or small. Each curve starts at the low seasonal month (at left), proceeds to the peak month and then returns to the same low month on the right. While the cases are few for most of the diseases, the chart gives a rough indication of the seasonal variation of attacks of the disease.

Of these chronic diseases, diabetes, prostate diseases, and sinusitis show the largest relative seasonal variation but other diseases such as rheumatic fever, heart diseases, and most of those in the left-hand column of Fig. 7 show just as regular seasonal patterns but with somewhat smaller relative seasonal differences between the low and high months of the curve. Most of the chronic diseases that have regular single-peak seasonal curves are at their highest in the winter or early spring months.

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HOSPITALIZATION

Hospital rates of admissions and of days of care are a measure of the severity of chronic disease as well as a measure of medical care.

Short-Term Care.—Hospital cases as recorded in family surveys are largely in short-term hospitals, although a few in other types are recorded. In Fig. 8 the total hospital cases of acute and chronic diseases are shown by age and sex, and by surgical and nonsurgical cases.

Considering acute and chronic surgical cases, it is seen that for each sex surgery is far more frequent on acute than on chronic cases; it is only after about 50 years of age that surgical chronic cases exceed the acute. On the other hand, nonsurgical chronic cases exceed nonsurgical acute cases after about 40 years of age, and at 65 years and over nonsurgical chronic cases among males are nearly equal to the high nonsurgical case rate under 5 years of age. Among females, chronic nonsurgical case rates are above those for acute cases after about 35 years of age if female genital and puerperal conditions are excluded.

Fig. 9 shows for the five surveys combined the extent and characteristics of hospital cases in terms of bar charts of actual rates for the fifteen most fre-

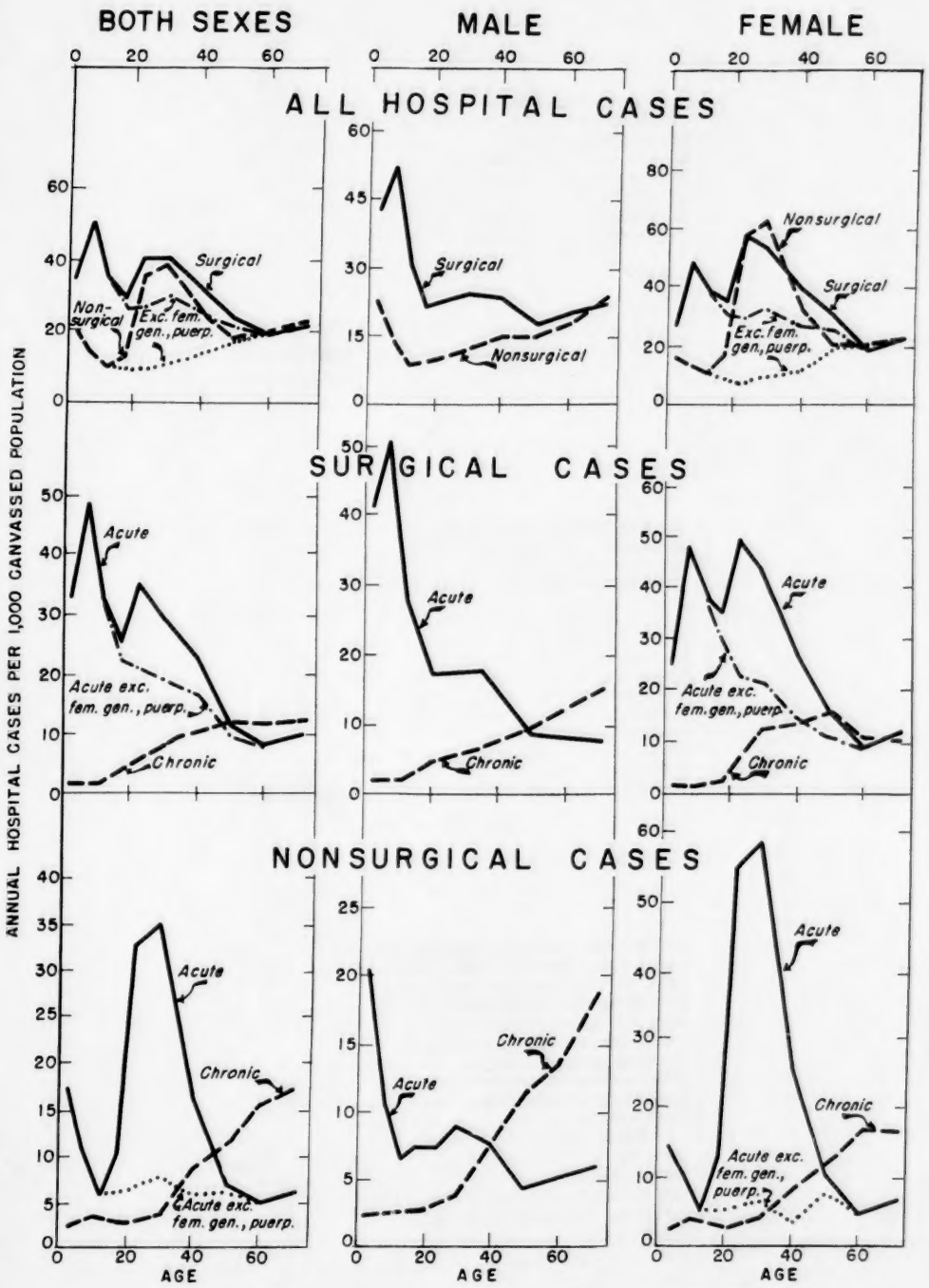
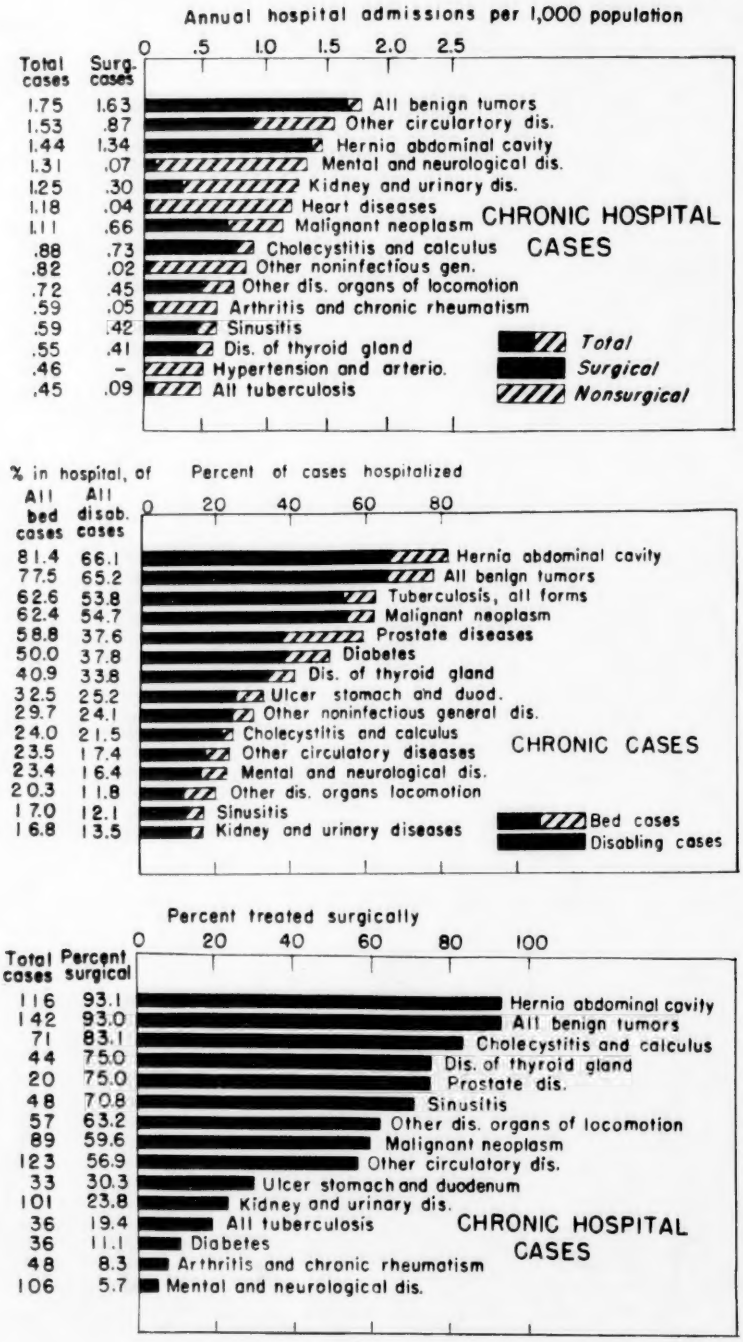


Fig. 8.—Annual age-specific hospital admissions per 1,000 males and females, classified into surgical and nonsurgical cases, with each category further classified into acute and chronic cases—five surveys with 80,768 full-time person-years of observation.


Annual hospital admissions per 1,000 population
0 .5 1.0 1.5 2.0 2.5
Total cases
Surg. cases
1.75 1.63 All benign tumors
1.53 .87 Other circulartory dis.
1.44 1.34 Hernia abdominal cavity
1.31 .07 Mental and neurological dis.
1.25 .30 Kidney and urinary dis.
1.18 .04 Heart diseases
1.11 .66 Malignant neoplasm
.88 .73 Cholecystitis and calculus
.82 .02 Other noninfectious gen.
.72 .45 Other dis. organs of locomotion
.59 .05 Arthritis and chronic rheumatism
.59 .42 Sinusitis
.55 .41 Dis. of thyroid gland
.46 - Hypertension and arterio.
.45 .09 All tuberculosis
CHRONIC HOSPITAL CASES
Total
Surgical
Nonsurgical
% in hospital, of
All bed cases
All disab. cases
Percent of cases hospitalized
0 20 40 60 80
81.4 66.1 Hernia abdominal cavity
77.5 65.2 All benign tumors
62.6 53.8 Tuberculosis, all forms
62.4 54.7 Malignant neoplasm
58.8 37.6 Prostate diseases
50.0 37.8 Diabetes
40.9 33.8 Dis. of thyroid gland
32.5 25.2 Ulcer stomach and duod.
29.7 24.1 Other noninfectious general dis.
24.0 21.5 Cholecystitis and calculus
23.5 17.4 Other circulatory diseases
23.4 16.4 Mental and neurological dis.
20.3 11.8 Other dis. organs locomotion
17.0 12.1 Sinusitis
16.8 13.5 Kidney and urinary diseases
CHRONIC CASES
Bed cases
Disabling cases
Percent treated surgically
0 20 40 60 80 100
Total cases
Percent surgical
116 93.1 Hernia abdominal cavity
142 93.0 All benign tumors
71 83.1 Cholecystitis and calculus
44 75.0 Dis. of thyroid gland
20 75.0 Prostate dis.
48 70.8 Sinusitis
57 63.2 Other dis. organs of locomotion
89 59.6 Malignant neoplasm
123 56.9 Other circulatory dis.
33 30.3 Ulcer stomach and duodenum
101 23.8 Kidney and urinary dis.
36 19.4 All tuberculosis
36 11.1 Diabetes
48 8.3 Arthritis and chronic rheumatism
106 5.7 Mental and neurological dis.
CHRONIC HOSPITAL CASES

A.

Fig. 9.—Extent of hospital cases and days of care, and other characteristics of hospital patients in terms of the fifteen highest chronic diseases for each characteristic—five surveys with 80,768 full-time person-years of observation.

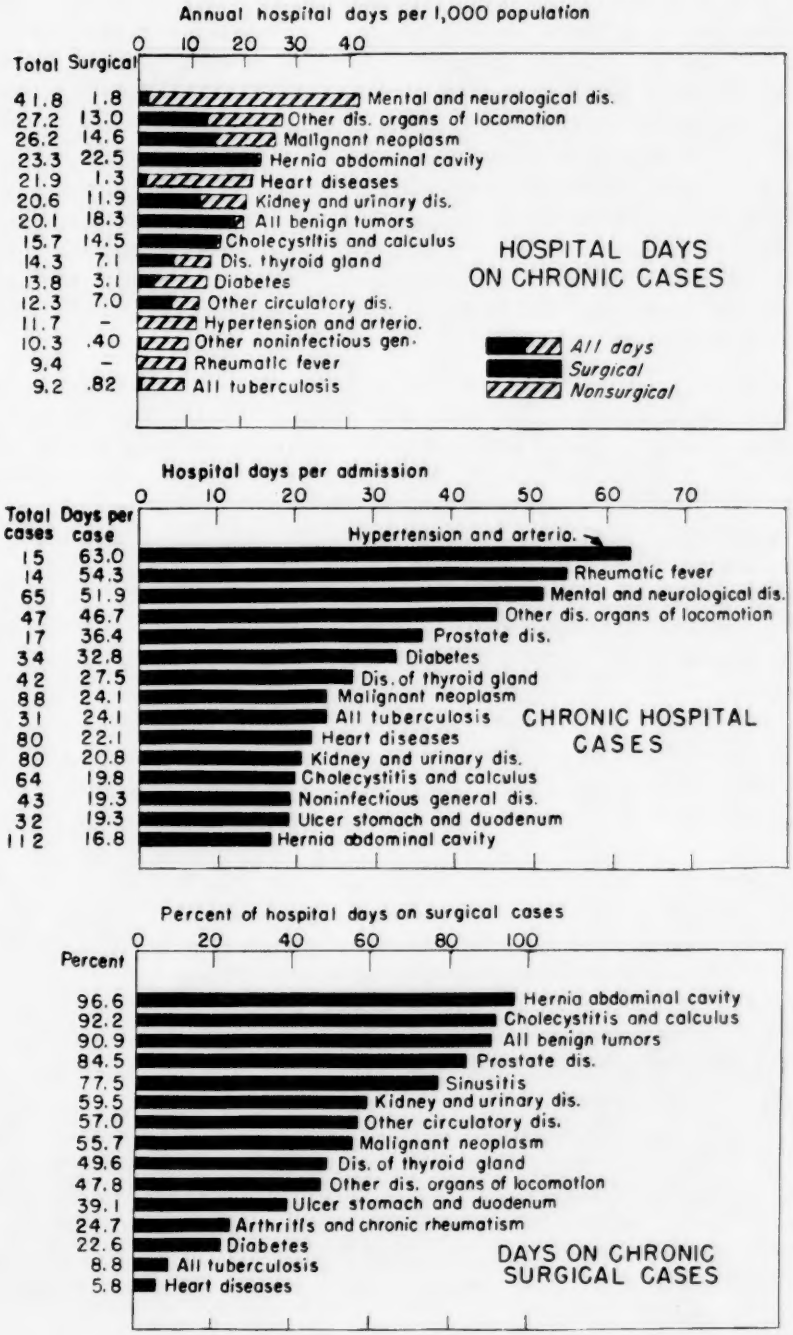

Annual hospital days per 1,000 population
0 10 20 30 40
Total Surgical
41.8 1.8 Mental and neurological dis.
27.2 13.0 Other dis. organs of locomotion
26.2 14.6 Malignant neoplasm
23.3 22.5 Hernia abdominal cavity
21.9 1.3 Heart diseases
20.6 11.9 Kidney and urinary dis.
20.1 18.3 All benign tumors
15.7 14.5 Cholecystitis and calculus
14.3 7.1 Dis. thyroid gland
13.8 3.1 Diabetes
12.3 7.0 Other circulatory dis.
11.7 – Hypertension and arterio.
10.3 .40 Other noninfectious gen.
9.4 – Rheumatic fever
9.2 .82 All tuberculosis
HOSPITAL DAYS ON CHRONIC CASES
All days
Surgical
Nonsurgical
Hospital days per admission
0 10 20 30 40 50 60 70
Total cases
Days per case
15 63.0 Hypertension and arterio.
14 54.3 Rheumatic fever
65 51.9 Mental and neurological dis.
47 46.7 Other dis. organs of locomotion
17 36.4 Prostate dis.
34 32.8 Diabetes
42 27.5 Dis. of thyroid gland
88 24.1 Malignant neoplasm
31 24.1 All tuberculosis
80 22.1 Heart diseases
80 20.8 Kidney and urinary dis.
64 19.8 Cholecystitis and calculus
43 19.3 Noninfectious general dis.
32 19.3 Ulcer stomach and duodenum
112 16.8 Hernia abdominal cavity
CHRONIC HOSPITAL CASES
Percent of hospital days on surgical cases
0 20 40 60 80 100
Percent
96.6 Hernia abdominal cavity
92.2 Cholecystitis and calculus
90.9 All benign tumors
84.5 Prostate dis.
77.5 Sinusitis
59.5 Kidney and urinary dis.
57.0 Other circulatory dis.
55.7 Malignant neoplasm
49.6 Dis. of thyroid gland
47.8 Other dis. organs of locomotion
39.1 Ulcer stomach and duodenum
24.7 Arthritis and chronic rheumatism
22.6 Diabetes
8.8 All tuberculosis
5.8 Heart diseases
DAYS ON CHRONIC SURGICAL CASES

Fig. 9 *B*. *(For legend see opposite page.)*

quent chronic hospital cases for: admissions and days of care per 1,000 population, per cent of patients hospitalized, days per hospital admission, the percentage of hospital cases treated surgically, and the percentage of hospital days on surgical cases. Although this is a large body of information to put in a single chart, it seemed worth while to put in the actual rates to supplement the many data plotted by age but on a more or less relative basis.

Fig. 10 shows admissions to hospitals for specific diagnoses as found in the five surveys. Because of small numbers and the fact that persons with minor illnesses are seldom hospitalized, it was possible to show by age only sixteen chronic diseases. With some exceptions the variation with age in these hospital cases for both sexes combined is similar to that shown in bed cases of the same diagnosis (Figs. 4 and 5).

Long-Term Care.—Family surveys are not particularly efficient in getting records of resident patients in hospitals for long-term care. Fig. 11 shows by sex and age, patients in long-term tuberculosis hospitals, excluding and including Federal hospitals, and patients in long-term hospitals for other chronic diseases except tuberculosis and mental diseases. The relative tuberculosis age curve for both sexes combined remains approximately the same when Federal hospitals are excluded. The curve for females alone is quite different from that for males, both with and without Federal hospitals. After about 35 years of age, the rates for males exceed those for females in both non-Federal and total tuberculosis hospitals, with highest rates at 50 to 60 years of age, which presumably represents veterans of World War I.

Rates for chronic diseases except mental and tuberculosis in long-term hospitals increase rapidly with age, with higher rates for males than females.

No discussion of chronic diseases is complete without consideration of the great body of patients with mental and neurological diseases and defects in special long-term hospitals and institutions for psychotic, mentally defective, and epileptic persons. The 1950 data collected by the National Institute of Mental Health[4] showed 722,508 resident patients in hospitals of these various kinds in the United States. Of the total of both sexes, 80 per cent were in long-term hospitals for mental diseases, 19 per cent in institutions for mentally defective and epileptic persons, and 1 per cent were in psychiatric services of general hospitals. In each of the three categories, about 53 per cent of the patients were males and 47 per cent females.

Fig. 12 gives a summary of age-specific rates of admission to these mental hospitals and institutions (except for psychoneurosis), and of resident patients in 1950. The rates are expressed as cases per 1,000 total population of the United States, to be comparable to other illness rates discussed in this review. Although the admission rates are small, they cumulate to a large total of patients in the United States receiving daily institutional care, with annual days of such care amounting to more than that given by all other types of hospitals in the United States.

The data in Fig. 12 include only broad classes of patients. Fig. 13 shows age curves for first admissions of specific kinds of psychoses, along with a few

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categories of persons with mental disorders without psychosis who have nevertheless been admitted to these hospitals for psychotic persons. First admissions for all epileptic and mentally defective persons without psychosis are shown

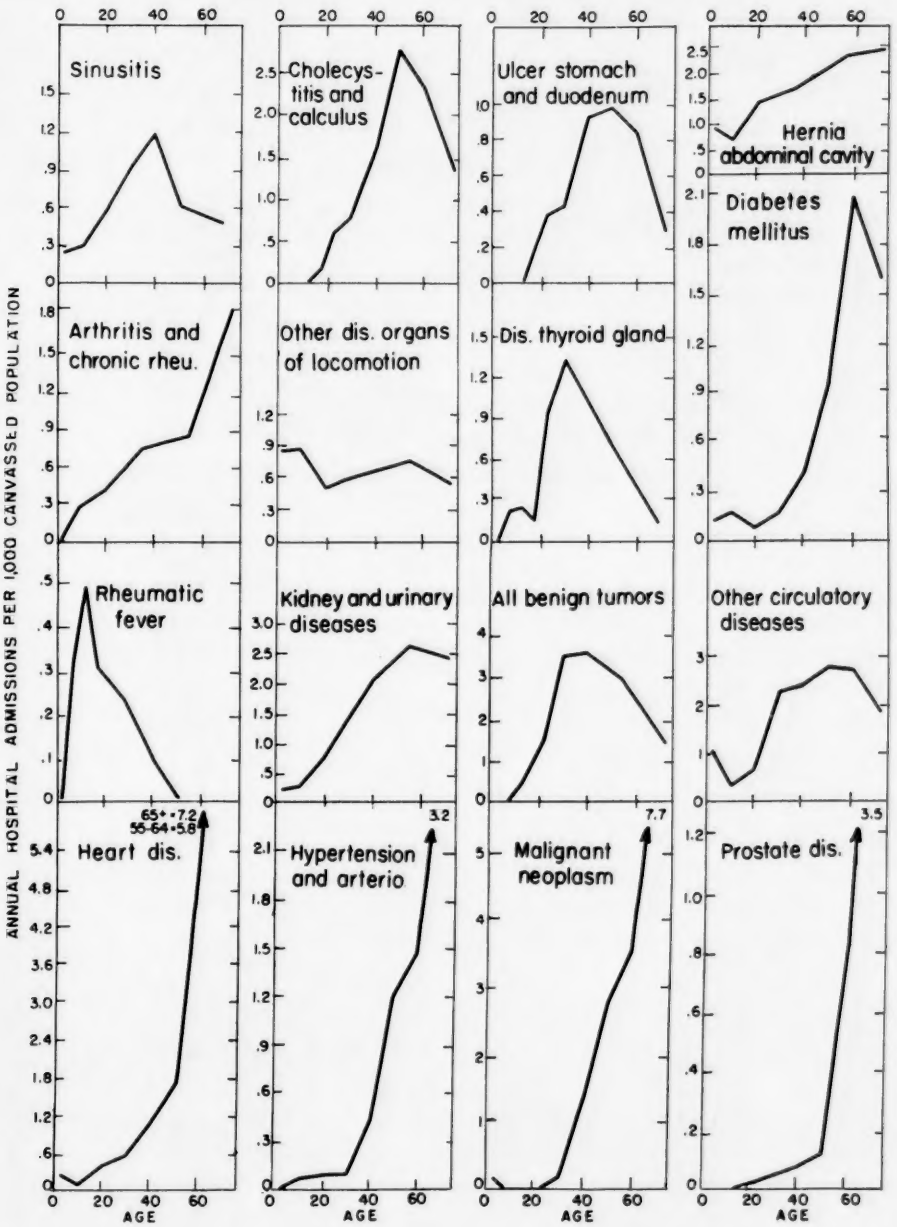
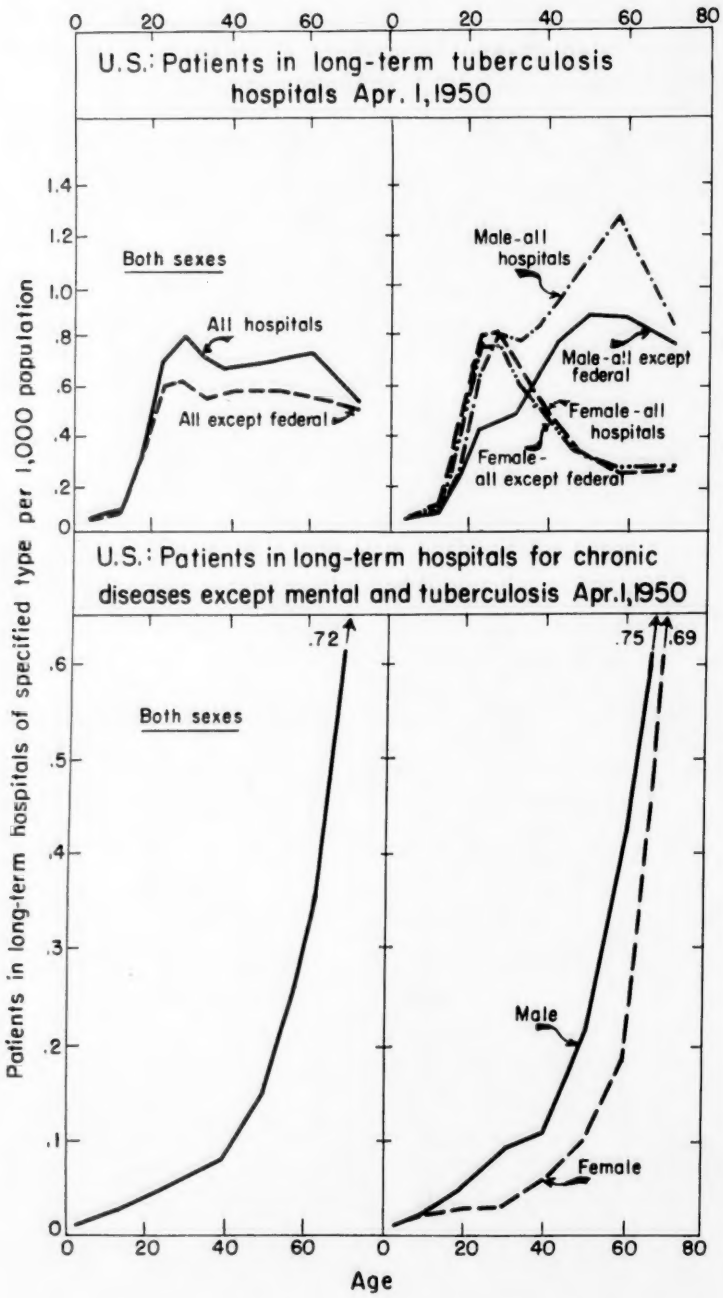


Fig. 10.—Annual age-specific hospital admission rates of chronic cases per 1,000 canvassed population, by detailed diagnoses—five surveys with 80,768 full-time person-years of observation.



A.

Fig. 11.—Age-specific rates of patients in long-term tuberculosis hospitals, and in long-term hospitals for chronic disease except mental and tuberculosis, United States, with comparative data for the five surveys.[11]

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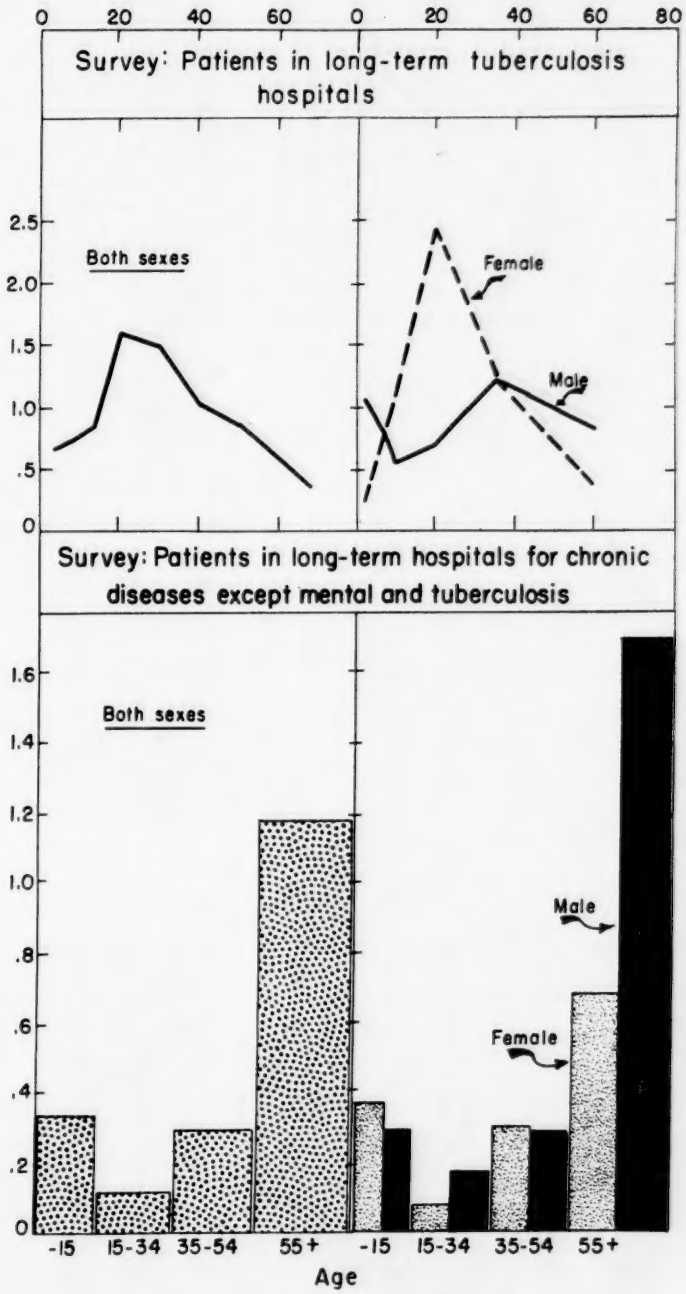

Fig. 11 *B.* *(For legend see opposite page.)*

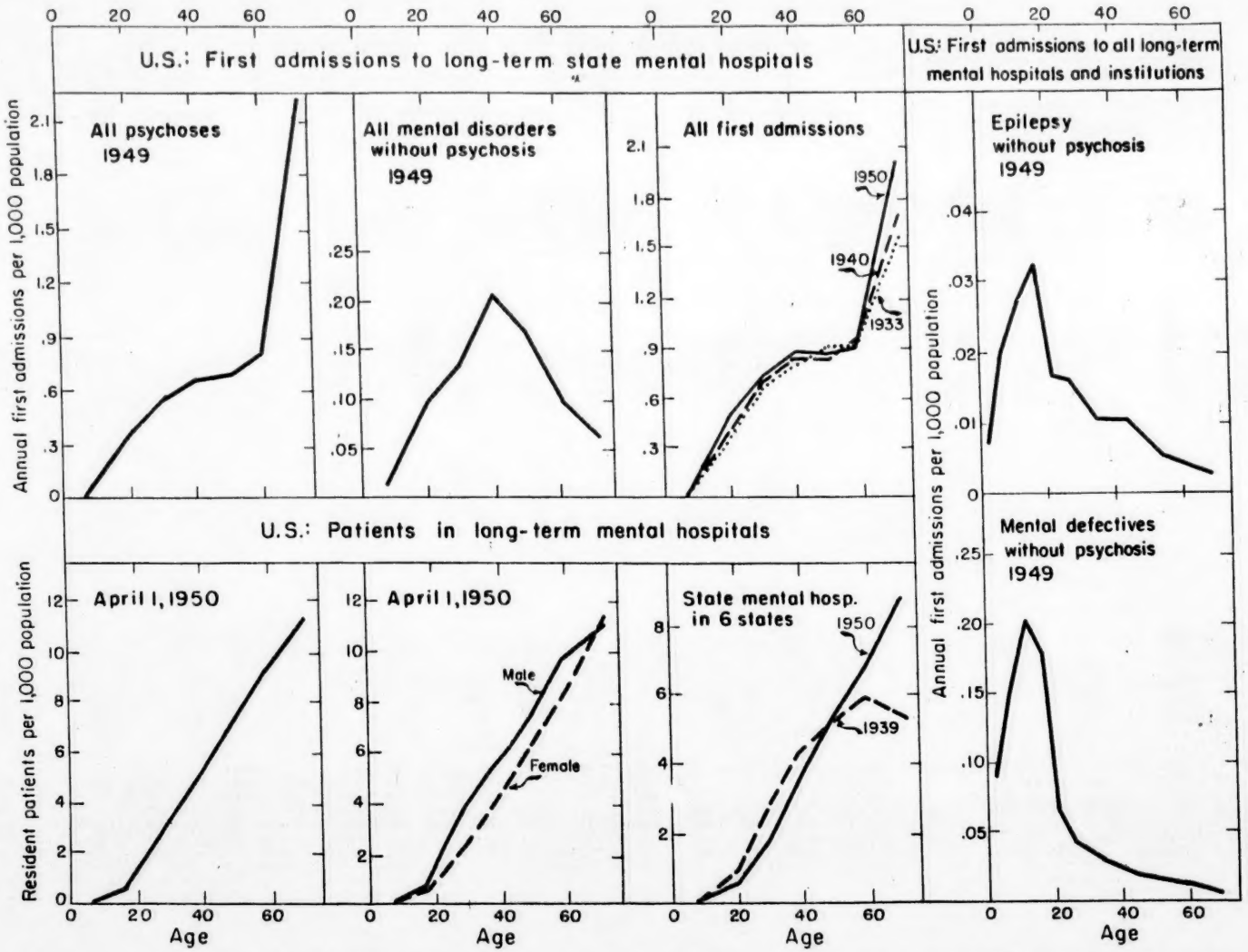

Fig. 12.—Annual age-specific rates of first admissions to mental hospitals, and patients in all long-term mental hospitals and institutions per 1,000 population, United States.[4,8,11]

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for all hospitals and institutions in the two curves on the right of Fig. 12. It is seen in this figure for the total United States that the peak of first admissions of mentally defective persons comes at 10 to 14 and of epileptic persons at 15 to 19 years of age, but the epileptic admissions at 10 to 14 are next to the highest rate for that condition.

Fig. 12 indicates that the highest first admission rate for all psychoses combined is for patients 65 years and older. Reference to Fig. 13 indicates that this peak is due entirely to psychoses of the senium (senile psychoses and psychosis with cerebral arteriosclerosis); all other psychoses except the miscellaneous and unclassified group have rates at ages 65 and over that are markedly lower than at earlier ages.

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TIME TRENDS

Trends of illness of any kind are hard to find, particularly of illness from chronic disease. Data on illness from all causes are available for United States Army personnel[5] from 1820 to the present but the great majority of Army personnel are young men who are usually free from chronic disease, not to mention the fact that they are medically examined to select the physically fit.

The various sickness surveys made over the past half century have made no pretense of following any pattern to give data comparable to those from any preceding survey. Even with the best set-up, it is extremely difficult to control the various techniques so that results in terms of sickness rates are comparable from one survey to another. Therefore about the only indices of the trend of illness are: (a) admissions to hospitals and institutions of various kinds for the care of the sick and defective and (b) death rates, of which it has been said: "It has long been known, from a variety of evidence, that morbidity and mortality do not connote the same things biologically. A person may have a great deal of sickness, continued intermittently over many years, and yet live to a ripe old age."[6] Nevertheless, deaths have been recorded in at least part of the United States for the past half century, with careful tabulations and analyses which, in the absence of illness records, are worth examining. During the period 1900-1953 the death rate from all causes has decreased from 17.19 to 9.59 per 1,000 population. At the same time the death rate from the noninfectious chronic diseases ("the great killers") has increased from 4.43 to 6.85 per 1,000 population, or to 71 per cent of the deaths from all causes in 1953.*

The trends of various other causes of death are plotted in Fig. 14 for the period 1900 to 1953. The total death rate is not plotted but the titles of the six cause groups that make up the total are underlined: chronic noninfectious diseases, acute infectious diseases, tuberculosis, syphilis and sequelae, rheumatic fever, and "all other causes." Other specific causes plotted on the chart are included in one of the six categories listed previously. Of the specific chronic noninfectious diseases on the chart, only nephritis shows a downward trend in the past quarter century; the others show an upward trend or no change in that

*Based on an estimate of the death rates from 1950 to 1953 according to the preceding International Classifications. Data for 1951-1953 are based on the 10 per cent sample.

time, including heart diseases, malignant neoplasms, cerebral hemorrhage and other cerebral accidents, diabetes, ulcer of stomach and duodenum, cirrhosis of liver, and hypertension and arteriosclerosis. The acute infectious diseases show a sharp downward trend (except for the great influenza pandemic of 1918), as do also the two chronic infectious diseases, tuberculosis, and, since about 1940, syphilis and sequelae.

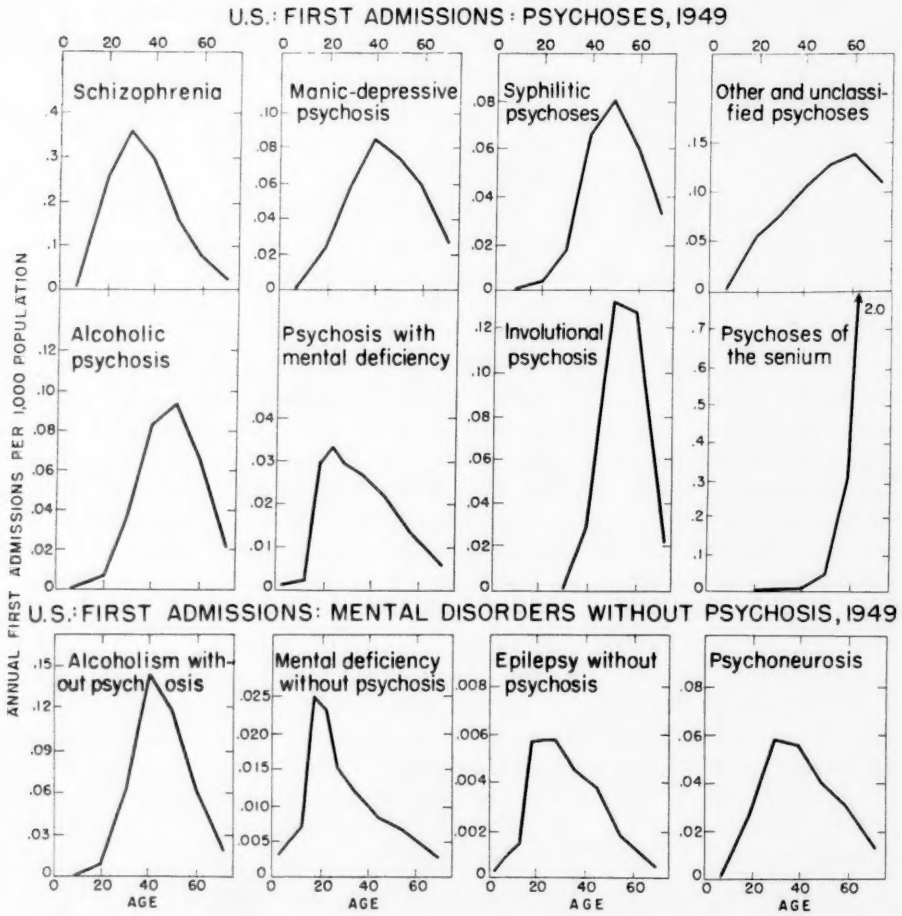

Fig. 13.—Annual age-specific rates per 1,000 population of first admissions to long-term mental hospitals, by specific psychoses and other mental disorders, United States, 1949.[4]

Cases in Hospitals of Different Types.—Fig. 15 shows trends of admissions to hospitals and institutions of various kinds in the United States. The data for all hospitals except tuberculosis, mental, and Federal, all mental and nervous hospitals, and all tuberculosis hospitals are based on reports published annually in the Hospital Number of the *Journal of the American Medical Association.*[7] For comparison, trends of death rates from all causes and from chronic non-

infectious diseases have been plotted from 1910 to 1953, but on a larger logarithmic scale than in Fig. 14.

Considering first the trend of admissions to all short-term hospitals (excluding mental, tuberculosis, and Federal*), as compared with that of admissions to long-term mental and nervous hospitals, the former increased 104 per cent during the period 1935 to 1953, as compared with 52 per cent for the latter. On the other hand, the increase in days of hospital care in the long-term mental and nervous hospitals during the same eighteen-year period was only 14 per cent, the average duration of the cases being so long that the relatively few admissions during a single year do not greatly change the average days from that of the already large number of accumulated cases in these long-term mental hospitals.

From the reports of the United States Census[8] and the National Institute of Mental Health,[4] it was possible to carry the trend of first admissions of epileptic and mentally defective persons from 1929 to 1949, but the data here shown are for a five-period moving average from 1931 to 1947. These data exclude the patients with diagnoses with psychosis but include those without psychosis in mental hospitals as well as in institutions for epileptic and mentally defective persons. The data are shown graphically in Fig. 15. Decreases in admissions to institutions for epileptic and mentally defective persons are often attributed to lack of available beds. However, patients in both categories are generally cared for in the same institutions but the data indicate that from 1932 to 1947 first admissions of epileptic persons decreased 37 per cent, as compared with 14 per cent for mentally defective persons.† This situation suggests that the newer treatments to prevent epileptic seizures may be decreasing the admission rates of epileptic persons to institutions.

In the lower right-hand chart of Fig. 15 there is a five-period moving average of admissions for mental disease to long-term mental hospitals of New York State from 1911 to 1951. Prior to 1924 there was little variation in average annual admissions, but from 1924 to 1944 the relative increase is less than in admissions to hospitals other than mental, tuberculosis, and Federal. After 1944, annual admissions to New York State mental hospitals increase very little.

Trends of admissions to and days of care in long-term tuberculosis hospitals as reported in the *Journal of the American Medical Association*[7] are also shown in Fig. 15. Tuberculosis admissions per 1,000 popuiation show irregular waves, but in total days of care there is an increase from 1935 to 1941, followed by a decrease to a minimum in 1947, after which there is a moderate increase to 1953, the last year with available data. This latter rise may be due to intensive case-finding compaigns by the mass x-ray technique. It may be seen in Fig. 14 that the death rate from tuberculosis shows no such rise as here noted in cases.

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*Federal hospitals show a large increase in admissions during World War II, so the exclusion of the Federal hospitals gives a more normal picture of the increase in admissions.

†The same situation of a greater percentage decrease in first admissions of epileptic than of mentally defective persons is found also in New York State alone, but in New York the two groups are cared for in separate institutions, so the decreases could both be due to lack of beds, as the report indicates.[9]

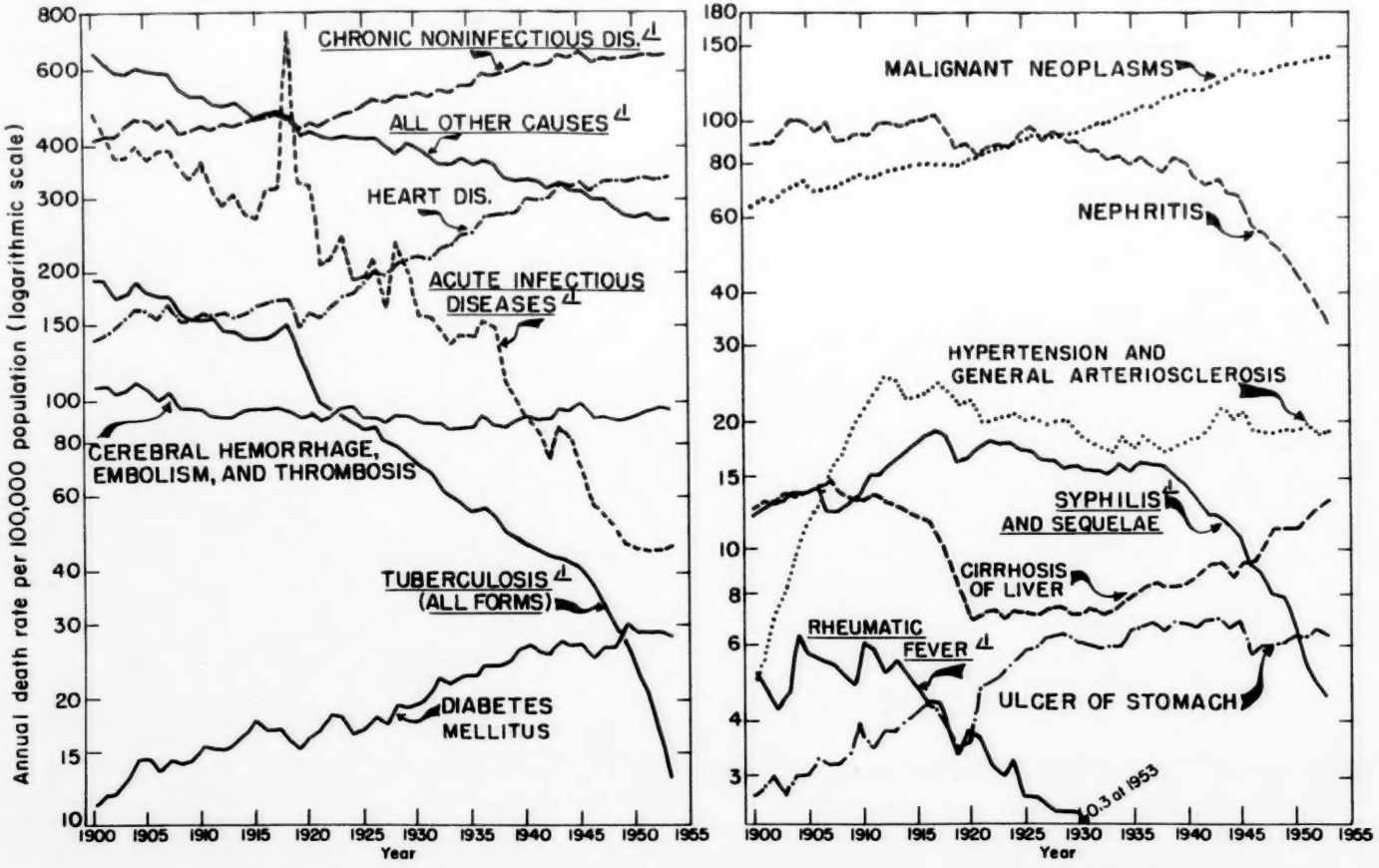

Fig. 14.—Trends of death rates from specific causes, 1900-1953, U. S. Death Registration States. (1950-1953 rates corrected to level of prior revisions of International List.[12,13] /1—These six cause groups make up the total for all causes.)

Hospital admissions of tuberculosis cases among active members of the United States Army decreased from 2.75 per 1,000 mean strength in 1930 to 1.22 in 1950, or 55 per cent in the twenty years. Meanwhile, death rates from tuberculosis in the United States Army decreased in the same period from 0.24 per 1,000 in 1930 to 0.019 in 1950, or 92 per cent.[10] The tuberculosis death rate among civilian males of similar ages (average of rates for ages 15 to 24 and 25 to 34) decreased from 0.816 per 1,000 population in 1930 to 0.138 in 1950, or 83 per cent.

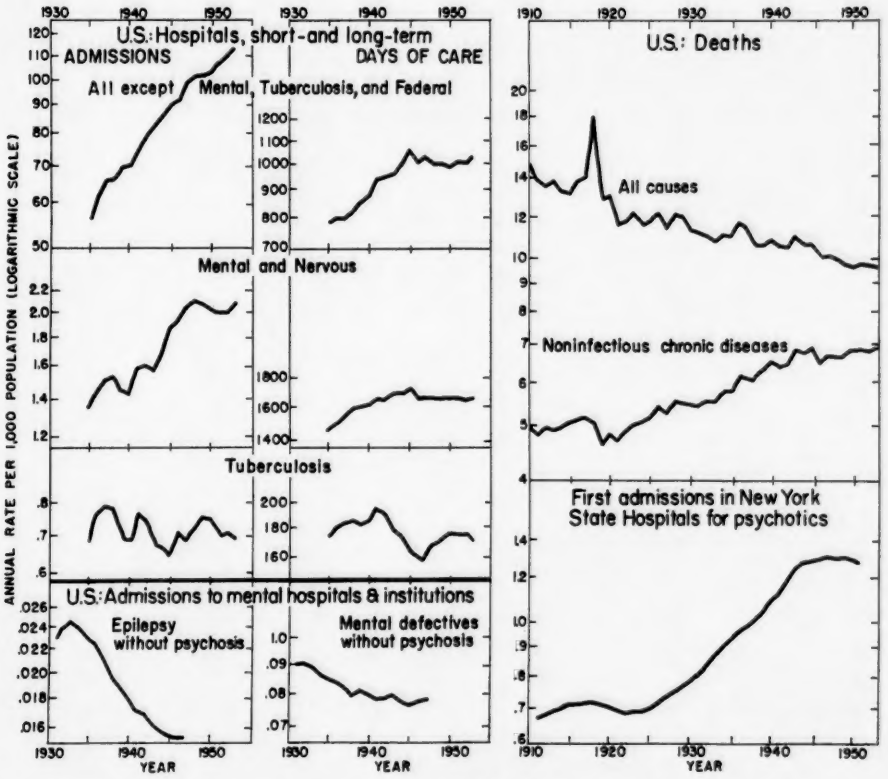

Fig. 15.—Trends of admissions to and hospital days in several types of hospitals and institutions from about 1935 to 1953, and trends of admissions to all New York State psychotic hospitals, with some trends of deaths in the United States, 1911-1950.[4,7-9] (Admissions to psychotic hospitals and institutions for mentally defective and epileptic persons are five-period moving averages.)

These and other data suggest that the long-time trends of sickness may have increased less or may have declined in the last quarter century, even though hospital care has increased.

Specific Psychoses.—Here, as in other illness data, there is more meaning to trends of admissions for specific psychoses than for admissions of all psychoses combined. Fig. 16 shows for seven specific and important psychoses the trend

(five-period moving averages) of admissions to New York State mental hospitals for both sexes and by sex for six of the psychoses. The psychosis that occurs most frequently, schizophrenia, is not shown by sex because the differences in the rates for males and females are not large. The relative increase in admissions for schizophrenia is less than in most of the psychoses that are increasing.

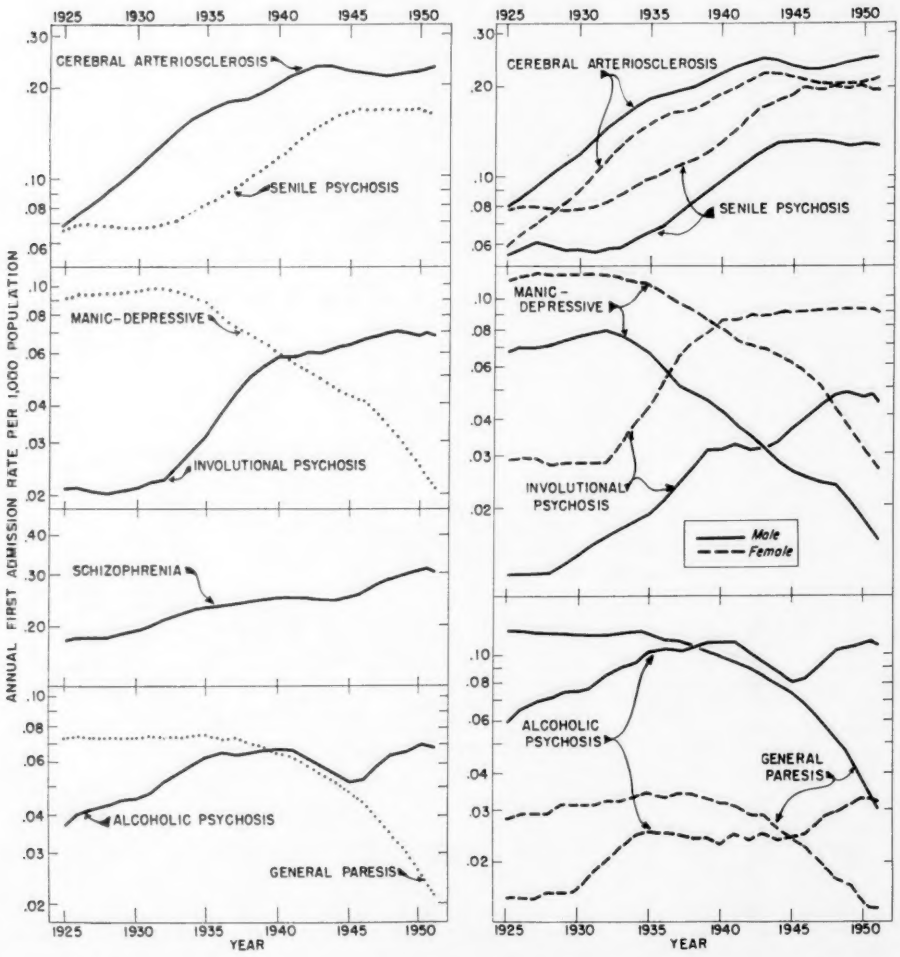

Fig. 16.—Trends of admissions (five-period moving averages) for specific psychoses to New York State mental hospitals, by sex, 1925-1950.[9]

Psychosis with cerebral arteriosclerosis and senile psychosis have followed reasonably similar trends, especially since about 1935; many psychiatrists combine them under the name of psychoses of the senium. Both increased until 1943 but after that time the rates are roughly constant. Both diagnoses show considerable sex differences, but cerebral arteriosclerosis admissions are more frequent among men and senile psychosis rates are higher for women.

Manic-depressive psychosis and general paresis are definitely on the decline since about 1935. Rates for general paresis are much higher for men than women, but the relative difference is less in recent years than formerly. Manic-depressive psychosis rates are higher for women than men. Alcoholic psychoses show, with some exceptions, a generally rising trend, with rates that are very much higher for men than women.

It is not intended in this discussion of trends of hospital care to suggest that such trends are an index of trends of illness in general. In fact there are conditions which increase hospitalization that have no particular relation to the trend of illness. For example, death rates have been on the decrease for many years but the proportion of all deaths in the United States that occurred in hospitals increased from 34 to 50 per cent in the years 1935 to 1949. The birth rate in the United States has been increasing and the proportion of live births that occurred in hospitals has increased from 37 to 88 per cent in the period 1935 to 1950. These and other conditions make for more hospital care but not for more illness in the community in general. Similarly, prepaid hospital care and payment for care of industrial accidents under compensation tends to increase hospital care without increasing the general level of illness.

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SUMMARY

This review of chronic diseases is based largely on data from periodic surveys of households made over a period of years, supplemented by data from long-term tuberculosis and mental hospitals and institutions.

Cases as here used represent attacks or episodes of illness that lasted for one day or longer. They are subdivided into (a) nondisabling with no time lost from usual activities, (b) disabling with one or more days lost from work, school, housework, or other usual activities, (c) bed, with one or more days confined to bed, and (d) hospital, with one or more nights in a hospital. Disabling plus nondisabling give the total, bed being a subclass of disabling, and hospital being a subclass of bed cases (Figs. 1, 2, 3).

Each chronic disease has its own characteristic variation with age. The majority of the diseases occur more frequently among women; some diseases stand out with very large excesses for women and a few with just as large excesses for men (Figs. 4, 5).

The attacks of chronic diseases show much less seasonal variation than attacks of acute diseases. However, many of the specific chronic diseases show characteristic seasonal variation (Figs. 6, 7).

While there is considerable surgery in chronic cases, there is much more in acute cases. Obstetric cases loom large in nonsurgical hospital practice (Fig. 8).

Average durations, relative age incidence, and other characteristics of hospitalized chronic illness vary greatly for different diagnoses. The relative age incidence in hospital cases of specific diagnoses is similar to that in bed cases of the same diagnosis (Figs. 9, 10).

Patients in long-term tuberculosis hospitals in the United States per 1,000 population show a peak for females at 25 to 29 years as compared with 50 to 60 years for men (Fig. 11).

First admissions of specific psychoses to hospitals for psychotic persons show peaks at various ages from 15-19 to 55-64 with definite declines thereafter, except psychoses of the senium with the highest rate at 65 years and over (Figs. 12, 13).

Death rates from the chronic noninfectious diseases have increased steadily in the last half century but the chronic infectious diseases have decreased rapidly (Fig. 14).

Admissions to the various types of hospitals have increased during the past fifteen to twenty years except admissions of epileptic and mentally defective persons, which have decreased, particularly for epileptic persons (Fig. 15).

Psychoses whose first admissions to New York State mental hospitals have generally increased since 1925 are senile, involutional, schizophrenia, alcoholic, and those with cerebral arteriosclerosis. Psychoses with a downward trend are manic-depressive and general paresis. Psychoses with higher admission rates for men than women are alcoholic, general paresis, and those with cerebral arteriosclerosis; those with higher rates for women than men are senile, involutional, and manic-depressive psychoses (Fig. 16).

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Appendix A

Confirmation of Diagnoses by Attending Physician

The diagnoses as reported by the household informant (usually the housewife) were entered on the schedules, together with the name of the attending physician and of the hospital if the patient was hospitalized. At the end of each round of the periodic visits, cases reported by the families as attended by a given doctor were assembled on another form, including the patient's name, age, sex, and other identifying information, the date of onset of the illness, and the diagnosis given by the family informant. The sheets for each doctor were mailed to him with a mimeographed letter explaining the nature and purpose of the study and requesting that he check the diagnoses that were correct and give the correct diagnoses for any that were wrong. Ample space was allowed for writing in the correct diagnosis. Although the letters were mimeographed, they bore the signature of the Surgeon General of the Public Health Service. The returns were good, but of course there was no way to check the diagnoses in unattended cases, and many other patients with mild cases had only a single visit to or from the doctor. Some diagnoses may have been checked from memory and others with little reference to records, but frequently the family informant was able to repeat what the doctor had said was the matter, even when she knew little about the disease. Although the attending doctor checked many symptomatic and some ill-defined diagnoses as correct, his diagnosis was always used in preference to that of the family informant when there was any difference between the two.

Appendix B

Distinction Between Acute and Chronic Disease

A statement on the method used in this study to distinguish between acute and chronic disease seems pertinent. The usual meaning of chronic disease refers to illness of long duration. In this paper, a disease or illness has also been classified as chronic if a history of one attack may be expected to be followed by other attacks of the same disease which are related to the preceding attacks because the patient was not cured but the disease was only quiescent between attacks. But so many patients with chronic disease have long periods without measurable disability that it seems appropriate to consider along with continuous total or partial disability these attacks

with relatively short periods of inability to be about usual activities and more serious episodes of illness requiring the patient to remain in bed at home or in a hospital.

The total time since the original onset of the chronic disease is important but so are the number of these more severe attacks and the total time unable to be about usual duties, the total days in bed, and the total days of hospital care. Records of all of these data, as well as of recovery or death, are necessary to measure the severity of a chronic disease in terms of time, inconvenience, and loss caused by a disease.

To cite a few examples, tuberculosis usually keeps a patient in bed at home or in a hospital for major parts of the day over long periods of time, and thus conforms to the usual definition of chronic disease as one of long duration. On the other hand, in many forms of heart disease the patient can do office or other light work for long periods without attack or other manifestation of the disease. However, a change to work involving greater stress and strain, either mental or physical, may cause the patient to suffer attacks which make him unable to work or be about other usual activities for a short or even a long period.

Asthma and hay fever are generally considered chronic diseases, although for considerable periods the individual may not be bothered by these diseases because the etiological factor is not present; if ragweed pollen is the causative agent, it would not be present except at certain seasons of the year and in certain latitudes. On the other hand, if house dust or some substance involved in the person's work is the etiological agent, these allergies would give almost constant trouble. In either case, the diseases would be classed as chronic.

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Review

THE NEPHROTIC SYNDROME

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THE nephrotic syndrome is a well-recognized clinical entity. The patient usually presents himself because of an insidious onset of edema. There is often no history of preceding illness. Occasionally a respiratory infection may have occurred just before the onset, but it is uncommon to find evidence of preceding streptococcal infection. The swelling may be preceded by gain in weight, but the edema soon shows itself in the ankles in the evening and in the face in the morning. On examination, the blood pressure is usually normal, the heart not enlarged. The skin looks puffy and pale; there may be a mild normocytic anemia. The blood proteins are grossly reduced, especially the albumin and gamma globulin fractions.[28,61,86] The cholesterol and fat in serum are elevated.[59,87] The urine contains much protein, mostly albumin. The urinary sediment in the early stages may be negligible, but later there are many granular and cellular casts, epithelial cells filled with fat, and sometimes free fat globules. Red blood cells are usually absent, but some patients show intermittent or continuous microscopic hematuria.

In contrast to the clarity and uniformity with which the syndrome is defined, there is a great deal of confusion concerning etiology, classification, prognosis, and treatment. In many cases of the nephrotic syndrome, the etiology is not clear. A picture resembling the nephrotic syndrome may occur in the course of several diseases, such as the nephropathy of diabetes mellitus, lupus erythematosus, amyloid disease, and thrombosis of the renal veins.[22,41,53,55] In these settings, the findings, course, and pathology are modified by the coexistent disease. In other cases, reactions of hypersensitivity to drugs or allergens, or glomerular nephritis,[10] may lead to a disease indistinguishable from the nephrotic syndrome.

There are many intimations that the nephrotic syndrome may be associated with some immunologic mechanism related to allergy. The most clear-cut examples are in those cases which follow respiratory allergens, poison oak, and

bee stings.[98,99] Tridione,[6,82,121] paramethadione,[123] bismuth,[7] and gold salts[115] have been reported to precipitate the nephrotic syndrome in certain sensitive persons. A large proportion of patients with the nephrotic syndrome have a history of allergic disease of some severity,[29,99] often related in time to the development of edema, and many of these patients show eosinophilia of a striking degree.[68] The specific mechanism by which these agents and reactions lead to the development of the nephrotic picture is not at all clear. Further evidence is furnished by the study of nephrotoxic serum nephritis, which will be discussed subsequently.

The relationship of the nephrotic syndrome to glomerular nephritis must be re-evaluated in the light of recent studies.[8,24,27] Since most patients who die after a prolonged course with the nephrotic syndrome show destructive glomerular lesions, it has long been conventional to classify these patients as having glomerular nephritis. Addis,[1] for example, assumed that all such patients started with an unrecognized attack of glomerular nephritis and proceeded through a latent phase to the degenerative stage (nephrotic syndrome), and thence almost invariably to the terminal stage of chronic glomerular nephritis. Nevertheless, Addis noted a substantial number of adults, as well as children, who showed a remittent clinical course and urinary findings, frequently ending in healing. He interpreted these observations as being incompatible with glomerular nephritis. There were minimal changes in the glomeruli in those patients who died early in the course of the syndrome. It was then suggested that abnormal plasma proteins could be filtered through a normal glomerulus to produce secondary tubular changes and the nephrotic picture. Addis pointed out the lack of urine sediment early in the course of these patients and the development of the characteristic degenerative phase as the proteinuria continued. The secondary nature of the tubular lesions seems to be generally accepted. Part of the proteinuria may be due to a failure of normal protein reabsorption by the tubules.

Most other observers have preferred the idea that the abnormality was in the filtering membrane and that the proteins in the serum and urine of patients with nephrosis are normal proteins.[39,61,62] In the earliest stage of disease, glomerular lesions may not be visible by light microscopy. In other cases, lesions that may not be obvious in the conventional hematoxylin and eosin stains may be brought more clearly to view by other stains.[8,91] Ellis[27] pointed out changes in the basement membrane, and more recently Ehrich, Forman, and Seifter[24] have emphasized thickening of basement membrane as the characteristic early lesion of the nephrotic syndrome. Whether these changes represent the basis of the protein leakage is still uncertain. There is, however, strong physiologic evidence that the glomeruli are abnormally permeable to serum albumin.[58,63]

It is apparent that the nephrotic syndrome can develop acutely without signs of glomerular nephritis, and that the essential lesion is an abnormal permeability of the glomerular filter to protein, which is reflected in changes in the basement membrane and secondary changes in the tubular epithelium. How should these changes be classified? Ellis[27] has pointed out the clear distinction in clinical course and pathologic picture between acute glomerular nephritis,

which he called Type 1 nephritis, and nephritis of insidious onset, chronic course, and fatal outcome, which he called Type 2. Ellis has also emphasized the changes in the basement membrane in Type 2 nephritis, in which the pathologic findings are indistinguishable from those of patients dying after a long-standing nephrotic syndrome.

Patients with a chronic nephrotic syndrome may develop persistent hematuria, failing renal function, rising blood pressure, anemia, acidosis, and uremia. When these patients die of renal insufficiency and hypertensive cardiovascular disease or encephalopathy, the glomeruli show an advanced picture of hyalinization and scarring. Such patients have been classified pathologically as having chronic glomerular nephritis, and this diagnosis has been extrapolated back to a hypothetical, unrecognized glomerular nephritis. It has been frustrating to work under this hypothesis, since it has been impossible to distinguish between those cases in which the patients were going to recover and those which would progress to renal failure. Neither clinical observation, examination of the urine and blood, nor the most detailed studies of renal function have been of much prognostic value.[3,4,79]

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These observations lead to the conclusion that the nephrotic syndrome is a separate clinical entity, which is not related to acute glomerular nephritis. In certain instances, the nephrotic syndrome heals, but other patients progress to renal insufficiency with glomerular scarring and hyalinization. Some insight into mechanisms of this process may be gained by serial renal biopsy and by study of experimental nephritis.

EXPERIMENTAL NEPHRITIS

The concept of nephritis as a disease of hypersensitivity led investigators to attempt production of a comparable lesion in animals. Of the variety of methods used in the production of experimental renal disease, bacterial injections alone or bacteria mixed with homologous kidney emulsions have been extensively studied, but a reproducible form of nephritis has not been obtained.[16] Intravenously injected heterologous proteins produce a proliferative renal lesion. However, this is accompanied by proliferative changes in other organs of the body. The disease is a systemic one, resembling serum sickness rather than acute nephritis.[25,45,60,93]

The most successful method of producing experimental renal disease is the use of nephrotoxic serum prepared by sensitizing an animal to renal tissue of another species. When this serum is injected into the species from which the kidney was obtained, antibodies are fixed in the kidneys and renal changes ensue.

Nephrotoxic serum prepared in fowl produces in dogs, rabbits, guinea pigs, and rats a disease characterized by latency of one week between time of injection and manifestation of symptoms.[26,35,50,76] The clinical course is one of oliguria, proteinuria, cylindruria, hematuria, moderate edema, and hypertension. Some animals die in uremia; others recover. Pathologically, there is predominantly endothelial proliferation of the glomerular capillaries with or without capsular exudation. This disease has been compared with acute hemorrhagic nephritis in man. The renal disease produced in rats by nephrotoxic rabbit serum is

characterized by immediate onset of symptoms: proteinuria, hyperlipemia, hypoproteinemia, and edema. Early workers compared this illness with nephritis.[107-109] In 1948 and 1951, Heymann and his associates[45] pointed out the similarity of this disease to the nephrotic syndrome as observed in childhood.

Current observations made with the aid of renal biopsy and weekly examination of autopsied material indicate that the type of disease produced in the rat is dependent on dosage and potency of nephrotoxic serum.[88] A small dose of serum produces in the rat a disease similar to that produced by nephrotoxic serum in the rabbit. Symptoms appear after a latent period of one week, and pathologically there are proliferative changes in the glomeruli. The rabbit does not survive larger doses of serum. The rat, however, responds to large doses with immediate onset of disease. The characteristic histologic change is thickening of the basement membrane of the glomerular capillary wall with or without exudation into the capsular space. A large portion of these animals die in renal insufficiency. It is of interest that the same immunologic technique can produce two experimental responses: one which resembles acute nephritis, and the other lipemic nephrosis. Such observations add considerable support to the role of hypersensitivity in nephrosis, as well as in acute hemorrhagic nephritis.

The renal lesion produced by heterologous protein depends on the ability of the antigen to reach the kidney, the ability of the recipient animal to produce specific antibody, and the antigen-antibody reaction in the glomeruli. Purified albumin produces less renal disease than globulin, probably because of its smaller molecular size, which allows it to be removed from the blood stream prior to reaching the kidney.[45,122] Hyaluronidase likewise lessens the renal lesions by facilitating the removal of the antigen from the blood stream.[103] Cortisone, x-radiation, nitrogen mustard, colchicine, and low-protein diet all inhibit the occurrence of nephritis, probably on the basis of their anti-inflammatory effect and interference in production of antibody.[18,81,92,102,103]

The renal lesion produced by nephrotoxic serum prepared in ducks also seems to depend on the ability of the recipient animal to produce antibodies. Kay[50] was able to inhibit formation of both duck serum antibody and renal lesions by irradiation of rabbits before injection of nephrotoxic duck serum.[50]

The influence of therapeutic measures in the disease produced in rats by nephrotoxic rabbit serum is difficult to evaluate because of disagreement in interpretation of the renal changes produced. Farr and Smadel[33] produced a disease which they compared with human glomerular nephritis. Nephrotoxic serum failed to produce disease in Whelan and Evans rats on a low-protein diet.[33] Hackel and associates,[43] comparing the disease with human nephrosis, saw no effect on the course of the disease with cortisone (5 mg. per 100 grams body weight twice daily) or ACTH (0.8 mg. per 100 grams body weight every six hours). Ehrich and associates[24] studied a few animals for two weeks using cortisone (2.5 mg. per 100 grams body weight) or ACTH (6 mg. per 100 grams body weight). The administration of this dose of corticotropin had no significant effect. However, previous preparation and continued therapy with cortisone after injection of nephrotoxic serum depressed edema, proteinuria, and the pathologic degenerative and proliferative changes. Cortisone in larger

doses appeared to aggravate the disease, but animals receiving cortisone alone showed hyperemia of glomeruli and proteinuria.[92] Nitrogen mustard has been reported to depress proteinuria of this disease, but no correlation was made with histologic changes.[12]

Because heparin has been reported to modify the clinical manifestations of nephrotoxic disease in rats[23,96] and to prevent the generalized Shwartzman reaction,[40] its effect was observed in a group of rats receiving potent doses of nephrotoxic rabbit serum and followed with weekly renal biopsy.[89] In animals receiving only nephrotoxic serum the procedure of biopsy in the first two weeks of the disease was found to produce glomerular capillary thrombosis and to increase the severity of the resulting pathologic lesions. This thrombotic phenomenon is similar to the capillary lesion of the Shwartzman reaction as described by Thomas and Good.[112] Heparin markedly decreased the occurrence of glomerular capillary thrombosis and diminished the renal response, whether heparin was given before the injection of nephrotoxic serum, two days after the serum injection, or four days after injection (the day after renal biopsy).

Although studies such as these are of great interest in understanding the nature of experimental renal disease, they are not to be interpreted as immediately applicable to treatment of human disease.

ADRENAL FUNCTION IN NEPHROSIS

When the quantity and biologic activity of known adrenal cortical hormones found in normal human blood are compared, it appears that the two most effective corticosteroids are aldosterone, which affects sodium and potassium balance, and hydrocortisone, which is most effective in maintaining normal carbohydrate metabolism, glomerular filtration rate, diuresis after water loading, and other functions.[36,90,97,100,105,120] If either hormone is present in excess, it may produce some effects ordinarily attributed to the other.[36,113] The secretion of hydrocortisone is regulated by pituitary corticotropin, while that of aldosterone is scarcely affected by the absence of the pituitary or by administration of corticotropin.[34,66,110] The output of aldosterone, on the other hand, is much increased during sodium deprivation without significant change in excretion of 17-hydroxy- or 17-ketosteroids.[67]

Aldosterone has a much higher biologic activity per unit weight than hydrocortisone or other glycogenic steroids. Thus the mass of chemically determined corticosteroids in blood, or their metabolites in urine, are thought to reflect variations in "glucocorticoid" excretion. Formaldehydogenic steroids, which are a rough but clinically useful measure of adrenocortical function, are excreted in normal amounts in the nephrotic syndrome. The response to stimulation with corticotropin is sometimes subnormal, especially in those patients who fail to show clinical improvement under treatment with corticotropin.[31,77]

When the nephrotic patient is treated with corticotropin or cortisone, there is a gradual increase in glomerular filtration rate.[5,68,70,80] A small increase is often seen in normal men treated with these hormones.[11] When there is a moderate depression of glomerular filtration in nephrosis, very striking increases may

be noted. There may also be a decrease in the abnormal permeability of the glomerulus to protein.[38,58] Such responsiveness serves as a measure of the reversibility of the renal lesion. Patients with far-advanced glomerular disease may not show this response.

The urine of edematous patients with nephrosis contains abnormally large amounts of sodium-retaining material,[21,68,70,77] which is also present in excess in the urine of patients with edema due to congestive heart failure, cirrhosis of the liver, toxemia of pregnancy, and some other clinical states.[13,14,21,69,74,106,116] The sodium-retaining corticoid from a patient with nephrosis has been identified as aldosterone,[75] and it seems probable that the active material is aldosterone in the other cases also. The excess of this sodium-retaining hormone in different patients, whose common difficulty is a failure of sodium excretion, offers circumstantial evidence that aldosterone plays a role in sodium retention and edema.[74]

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The high level of aldosterone in the urine falls when improvement of the nephrotic state results in diuresis and elimination of sodium.[68,70,77] This reversion toward normal levels of aldosterone and sodium in the urine has been observed after spontaneous diuresis, or during treatment with concentrated human serum albumin, or following administration of cortisone or corticotropin. When the same therapeutic measures are not followed by diuresis, sodium-retaining activity of urine remains high. This inverse relation between aldosterone output and urine sodium is independent of changes in urine volume induced by changing water intake and is not directly dependent on changes in proteinuria.[68,70,74] These observations suggest that the level of aldosterone is increased during exacerbations of the nephrotic syndrome, perhaps by reduction in plasma volume and inadequate circulation,[85] and is reflected in decreased sodium excretion. The effects of corticotropin and cortisone appear to be mediated by changes in the underlying physiologic disturbance and not by direct stimulation or suppression of adrenocortical secretion of aldosterone.

Histologic evidence, collected by Deane and Greep,[19] suggested that the sodium-retaining hormone of the adrenal cortex originated in the zona glomerulosa of the adrenal cortex. Rats maintained on a diet low in sodium showed hyperplasia of this zone.[20] Similar changes were found by Peschel and Race[84] in the adrenals of patients who were deprived of sodium for several months. Gifford[37] had observed unusually large cells filled with small lipid droplets in the zona glomerulosa of two patients who died of acute intercurrent disease during the nephrotic syndrome. Since the output of aldosterone is increased under these circumstances, such histologic changes suggest that aldosterone may originate from the zona glomerulosa.

The effects of a high level of aldosterone on the renal lesion and on proteinuria remain to be explored. There is evidence that other adrenal hormones may increase proteinuria in experimental animals and in patients with nephrosis.[2,68,70] Antagonism may exist between the effects of "mineralocorticoid" (desoxycorticosterone) and "glucocorticoid" (cortisone) on certain vascular and connective-tissue reactions.[104] This question must be re-examined, since aldosterone is both highly effective as a "mineralocorticoid" and also capable of acting like a "glucocorticoid" in larger doses.[36]

The idea that nephrosis is a metabolic disease, perhaps arising in the adrenals, does not appear tenable. However, it is clear that changes in adrenocortical activity may modify the course of the nephrotic syndrome.

MANAGEMENT

The management of the nephrotic syndrome includes, first, measures for the improvement of the patient's general condition and, second, efforts to minimize progressive renal damage.

There is no indication for prolonged bed rest or hospitalization. It may be desirable to hospitalize for initial studies and for treatment of specific problems. A few days of rest in bed may help to mobilize edema.

A diet low in sodium is recommended, since these patients excrete sodium with great difficulty. An intake between 2 and 3 Gm. of sodium chloride may be best for many patients, especially during periods when there is a marked tendency to accumulate edema. If sodium restriction is followed by constant or falling weight, there is little to fear, but if fluid continues to accumulate on a very low sodium intake, the risk of a low-sodium syndrome is considerable.[42,80,101]

The protein content of the diet has been the subject of much debate.[1,4,3] Epstein[28] first pointed out the protein deficiency which frequently accompanies the nephrotic syndrome. General emaciation often becomes apparent after loss of edema fluid. The question remains whether a high-protein diet should be used to correct this deficiency, or whether the use of such a diet adds unduly to the work of the kidneys. It seems obvious that an adequate protein intake must be supplied, and that sufficient calories must be given in carbohydrates and fat to allow the desired gain in weight and storage of protein. In this way, positive protein balance can often be achieved without resort to diets of excessive protein content. In general, the chief problem is to maintain adequate nutrition in a sick patient. Encouragement and minimal restrictions should achieve this end.

Fluid intake should be adequate to ensure ample flow of urine. Restriction of water intake has only slight effect on accumulation of water in the body and leads to undesirable retention of urea, potassium, and other substances in the blood and body fluids.

Infection is a major hazard to the patient with nephrosis. Therefore, he is advised to restrict contacts to a minimum, without complete isolation. He should avoid exhausting exercise, severe chilling, and factors which might make him more susceptible to infection. Routine antibiotic therapy has not been generally used. The continuous use of antibiotics leads to a reduction in the incidence of secondary infection,[17] but the invaders are often bizarre and resistant organisms which make the treatment of intercurrent infection much more difficult. The alternative is to administer antibiotics only when signs of infection appear. In this case the antibiotic should be one to which the patient is known not to be sensitive, and the patient should have a supply on hand so that he can begin its administration at the first symptoms of infection. It may be better to use prophylactic therapy during the winter and in patients who are

having frequent infection. Therapeutic doses of a broad-spectrum antibiotic are given routinely during intensive courses of adrenal hormone therapy.

A number of measures have been proposed for the relief of edema in the nephrotic syndrome. In the presence of massive edema, which in itself sometimes seems to be a barrier to diuresis, paracentesis may give relief. Southey's tubes have been used with good results. Concentrated human serum albumin[48,72,73] and other agents[44,47,83,117,119] which increase blood volume, renal circulation, and diuresis are also very helpful. The administration, for example, of 50 Gm. of albumin daily results in elimination of much edema in approximately one-half of the patients who are so treated for four to seven days. The initial response is a diuresis of water, reduction in the level of blood urea and potassium, and increase in the serum sodium concentration toward normal. Even if the diuresis induced by albumin is not a large one, this measure may assist greatly in the correction of electrolyte problems.[65]

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Other agents not only relieve edema but may result in more fundamental changes in the course of the disease. The occurrence of diuresis after an acute infection, and less frequently of remission of proteinuria and all evidences of disease, has been known for a long time. Measles may be induced in nonimmune children with good results.[49] Improvement of the nephrotic state may follow hepatitis,[9] dengue fever,[118] malaria,[11a,35a] or the administration of yellow fever vaccine or influenza vaccine.[95] Treatment with nitrogen mustard[15,52,111] has also accomplished similar results. None of these agents appears to be as innocuous or as easy to use as the adrenal hormones.

When corticotropin or cortisone is given to a patient with the nephrotic syndrome,[5,30,51,68,70,71,94,114] there is an initial retention of water with oliguria and decrease in serum sodium concentration if the patient is on a very low sodium intake. A rise in the serum potassium concentration may occur at the same time. A small increase in blood pressure occurs regularly at this time. In a few patients, a marked rise in blood pressure, associated with headache, convulsions, coma, oliguria, and hyponatremia, has been observed. Fortunately, such severe reactions are rare.

At the end of about one week of therapy, renal function begins to improve, urine flow increases, and edema decreases. In some patients receiving corticotropin, there may be decrease in proteinuria and delivery of edema during the second week of treatment. The serum potassium concentration may fall abruptly under the combined influence of diuresis and adrenal hormones. When diuresis appears, potassium chloride should be given in dosage adequate to control the hypokalemia. More often, diuresis appears after the end of ten to fourteen days of hormonal therapy.

Such brief courses of hormonal therapy result in diuresis in approximately three-fourths of the cases. Proteinuria usually decreases during diuresis. In one of five cases, the abnormal proteinuria disappears completely. Response to hormone therapy may be blocked by intercurrent infection. A second or third course of therapy, given within two weeks of the preceding course, increases the incidence of diuresis and reduced proteinuria.[54,71]

Brief interruption of hormone administration may be beneficial, since improvement occurs as often after withdrawal of corticotropin or cortisone as during administration of hormone. Prolonged periods of time without hormone are followed by increased frequency of relapse. At the end of six to twelve months only a few patients still show improvement.

Previously, hormone was given only when edema appeared and when the patient's general condition appeared to be deteriorating. The frequency of relapse, the tendency of the renal lesion to persist or progress, and the gradual development of resistance to the effects of adrenal hormones have been drawbacks of this form of treatment.

Long-term therapy has been suggested to avoid some of these problems. Lange and his collaborators[56,57] have prescribed oral cortisone (100 mg. every six hours) on three consecutive days during each week, no therapy being given on the other four days. This plan has the advantage of avoiding the more objectionable features of Cushing's syndrome, as well as the adrenal atrophy which follows continuous therapy with cortisone. It may also take advantage of improvement on withdrawal of hormone as well as the benefits of high levels of circulating 17-hydroxycorticosteroids. This form of therapy has been used successfully for long periods. Lange[57] reported that twenty-eight of twenty-nine patients were free of edema after three to forty months of treatment. There were no serious side effects from the large dosage of cortisone. Children often developed a voracious appetite and some roundness of the face. No evidence of retardation of growth was seen. Proteinuria fell slowly and irregularly to low or normal levels. There is no agreement as to how long treatment should be continued. Of six patients, treated similarly for three to eight weeks, relapse occurred in three following discontinuance of hormone.

Of five children in our own clinic who received only 25 mg. of cortisone every six hours for three days of each week, only one has remained free of edema while on treatment. The larger dosage used by Lange appears to be essential to prevent relapse. Since almost all recurrences follow respiratory infection, it is possible that cortisone, 100 mg. per day, might suffice in periods without stress, but the dose should be increased to 400 mg. per day to avoid recurrence during and following respiratory infection. Infection should be treated promptly and vigorously with an appropriate antibiotic.

If proteinuria and edema reappear during adequate maintenance treatment, it is not necessary to modify therapy for one or two weeks. If spontaneous improvement does not ensue, it is advisable to use large and continuous doses of ACTH or cortisone for seven to fourteen days or until diuresis occurs. Intermittent administration of cortisone may then be resumed.

Other investigators believe that these patients should be treated like any other patient with chronic disease of connective tissue. For children, Merrill[78] recommended daily corticotropin gel (1 mg. per pound body weight) until edema and proteinuria are eliminated. The same amount is then given every other day for two weeks, followed by very gradual reduction of dosage for twelve weeks. If improvement is maintained, the frequency of injection is decreased to twice a week for four additional weeks. Such a program inevitably produces evidences

of hyperadrenocorticism with all of the attendant risks. Merrill does not feel that the results of this plan of treatment justify the serious side effects which occur in adults. Children are given a diet very low in sodium, as well as supplements of potassium salts (6 to 10 Gm. per day). Probably the most serious danger concerns the masking of infection, which is frequent in patients with nephrosis under any circumstances. Sulfadiazine (0.5 Gm.) is given daily, and coryza or other intercurrent infection is treated promptly and vigorously with penicillin or a broad-spectrum antibiotic. The patient is examined daily, with special attention to ears, chest, and abdomen. If recurrence of proteinuria or edema follows infection or other cause, the dose of corticotropin is doubled. If improvement does not appear within a few days, the initial plan of intensive treatment is reinstituted.

The patients treated by Merrill according to this plan have responded with diuresis and reduction of proteinuria and have maintained this improvement for many months. Of twenty-four patients so treated, twenty-three are alive and free of edema for one to eighteen months after treatment. One patient has become resistant to hormone therapy.

All plans of treatment include the initial use of corticotropin or cortisone in high dosage for about two weeks. Subsequent treatment depends to some extent on the result of this initial course, which may be used as a measure of responsiveness to the adrenocortical hormones. In each case, a plan of therapy should be laid out for at least six months, since long intervals without hormone administration have allowed frequent relapses, development of resistance to therapy, and renal failure. The program recommended by Lange[57] is suitable for the majority of patients. Because of practical considerations, long-term continuous treatment with corticotropin is reserved for unusually resistant cases.

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Editorials

OBESITY AND HEART DISEASE

Public alarm about the increasing dominance of heart disease in our national mortality produces great pressure for control and prevention programs. That preventive measures against heart disease are sorely needed is obvious to laymen and doctors alike, but the urge to set up prevention programs is likely to be accompanied by wishful thinking and glib talk.

The prospects are bright for real accomplishment from preventive programs directed against rheumatic heart disease, and some reduction in the frequency of congenital cardiac abnormalities may be expected from the control of prenatal infections of the mother during gestation. Efforts in these directions are already under way. But what about other forms of heart disease? After all, the current public alarm and professional concern about the prevalence of heart disease are primarily based on the distressingly large total cardiac mortality in this country, and at least 90 per cent of our heart disease deaths are not attributable to rheumatic fever and congenital defects. As a matter of fact, over three-quarters of the total cardiac mortality reflected in our latest statistics (1951) is attributed to arteriosclerotic heart disease and myocardial degeneration. Add hypertension and we have accounted for 86 per cent of the mortality cost of heart diseases. Now what will be offered for this overwhelming proportion of our total problem? The preventive measures that come to mind are three: periodic medical examinations, general advice on how best to live, and the control of obesity. The first two of these can be disposed of quickly.

Medical "checkups" are urged on the general principle that the early detection of disease will allow more effective treatment and that in any case periodic exposures to the good advice of the physician will be useful. In so far as actual disease is discovered and treatment is instituted, "health examinations" can be endorsed, but such early diagnosis is far from being real prevention.

The value of the good advice of the physician can be judged by considering the nature of that advice. And it should be observed that in regard to the prevention of heart disease, the advice of the personal physician corresponds to the precepts available for other methods of education and propaganda which might be used in preventive programs. By and large, these precepts are common-sense generalities—"don't overdo things," "practice moderation in all things," "avoid violent emotions," "stop smoking" (maybe), "get a good vacation every year," and so on. These platitudes are harmless and even admirable, but there is not the slightest guarantee of their virtue for the prevention of heart disease.

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Among the items of good advice offered by the family doctor and in all programs suggested to prevent heart disease is the injunction against obesity. This is much more positive and concrete than the other admonitions and it is actually the only item in the list for which persuasive evidence has been offered.

Belief in an important relationship between obesity and heart disease is so firmly rooted that it is seldom critically examined. There are two distinct questions: Does obesity predispose to heart disease? Is the control of obesity desirable for the cardiac patient?

The answer to the second question is certainly "Yes!" but it does not necessarily follow that obesity produces heart disease. Obesity has few merits but, besides condemning it in general, it is essential to ask precisely what the control of obesity may contribute in the fight against heart disease.

The real evidence against obesity is largely from the experience of life insurance companies; but ready acceptance of the idea that the control of obesity would go far toward controlling and preventing heart disease has several bases, particularly in moral and esthetic concepts. It is widely believed that obesity is the bodily evidence of self-indulgence, hence at least faintly immoral and inviting retribution. Conversely, the reduction of obesity and the avoidance of the temptation of gluttony implies self-denial which ought to bring rewards, appropriately including good health. This moral attitude is reinforced by esthetic considerations; obesity is unsightly.

Medical practitioners share these general persuasions and add points from their own professional experience. Surgeons are disturbed by the mechanical interference of the adipose tissue they encounter. Internists see benefits from obesity control in their patients with diabetes and hypertension. Moreover, physicians, like politicians and other folk, always distrust any departure from the general norm of the population, and gross obesity is such a departure. But experience in the treatment of sick patients is not necessarily relevant to the prevention of heart disease; and it is dangerous to assume that nonconformity with the average of the population always bodes ill for future health.

There is no intention in the present discussion to defend obesity, but we must examine the evidence critically before promising that the correction of obesity in the population will have a major effect on the incidence and mortality from heart disease in that population.[12]

It cannot be doubted that obesity and the excess metabolic cost of moving the overweight body may be a serious strain on a diseased heart. The efforts of the physician to make his fat cardiac patients reduce make very good sense. But the implications for the healthy heart are something else, and the maintenance of the argument against energy expenditure in general could logically lead to the condemnation of all exercise for everyone. Confusion between the management of heart disease and its prevention easily results in absurdities.

In the modern condemnation of obesity, much has been made of the wisdom of the Hippocratic doctors in recognizing an unusual frequency of sudden deaths among corpulent men, but these same doctors "recognized" many tendencies which are now completely discredited. In any case it is arguable whether obesity per se causes this tendency toward sudden death or whether, perhaps, men who

are prone to sudden death are also and independently prone to become obese. Two other questions may be asked: Is sudden death actually much more frequent among obese men? There is singularly little documentation for a claim upheld for some twenty-four centuries. And is *heart* disease the cause of all the sudden deaths?

Without lingering over these specific questions, it is instructive to examine the insurance statistics so ably assembled by Dublin, Armstrong, and their colleagues.[1,5,6] They deal with the mortality experience of policy holders who were 20 to 75 per cent overweight in comparison with the average "standard risk." In comparison with the standard risks, these overweight persons, in the first twenty years after policy issue, proved to have a death rate excess of some 50 per cent for all causes and almost the same excess for deaths from heart diseases. The outcome is justification for the high extra premiums charged on such policies.

The first criticism, that these data merely show an association between overweight and excess cardiac mortality without evidence for a causal connection, is answered at least in part by finding an improved mortality among men who originally paid penalty premiums because of gross overweight but who managed to get their insurance rerated by reducing and staying that way.

All of this is impressive, but it still is proper to ask whether the correction of overweight in our population would actually go far toward preventing our excessive mortality from heart disease. That our present mortality rates are excessive in the age range up to 70 is shown by a comparison of the age-specific mortality rates in the United States with those in many other countries.[9,11,13] The death rates of American men from the total of all causes are higher than for men of the same age in most other comparable countries, and this unfavorable situation is explained by a great excess of mortality from degenerative heart disease.

In 1950, for example, 108,630 white men aged 50-59 died from all causes in the United States. If these men had experienced the 1950 death rate of men of the same age in Italy, only 87,795 of them would have died. When the deaths ascribed to degenerative heart disease are compared, our white men aged 50-59 show an excess of 25,173 deaths compared with the Italians, and that is more than enough to account for our poor total showing. The question is whether the elimination of obesity among our men could correct our excess mortality.

From insurance company estimates it is possible that as many as 7 per cent of our men have that degree of overweight which, in life insurance experience, is associated with seriously unfavorable mortality. A little arithmetic based on these data shows the possible benefit if none of our population was as much as 20 per cent overweight. For all causes of death the indicated reduction in mortality of men aged 45 is 5.0 per cent, of men aged 55 is 3.8 per cent, and of men aged 65 is 3.4 per cent. For deaths from all heart disease the calculation is less certain; but roughly the elimination of all our men now 20 or more per cent overweight might result in a heart disease death rate for 55-year-old men 2.6 per cent less than the experience of our 55-year-old men as they are now.

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These calculations indicate the possible effect of the correction of our gross overweight. The prospective gain is disappointingly small. Instead of a total mortality excess, compared with Italy, of 23.7 per cent for men in the fifties, our excess would be 19.0 per cent. Moreover, this does not consider the fact that Italians, too, are often grossly obese.

It should be noted that the example of comparison with Italy could be replaced, with similar results, by comparison with England and Wales, Sweden, and various other countries. The upshot is that American men suffer a serious excess of heart disease and that weight control offers no prospect for correction of more than a small part of this. Moreover, even this evaluation may be overly optimistic.

There is a troublesome question about the overweight persons who pay extra premiums for life insurance and whose mortality experience is cited. Such persons make up some 2 per cent of the policy holders, although it is claimed that about 7 per cent of the national population is similarly overweight.[1] If only one of three grossly overweight men finds representation among the policy holders, do the insurance companies get a fair sample?

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There is an interesting parallel in the history of women versus men as insurance risks. Formerly women paid higher premiums than men because their mortality experience, as insurance policy holders, was distinctly unfavorable. This was in the days when relatively few women sought to carry life insurance. With changes in insurance practices which attracted a much bigger representation of women into the policy-holder class, the unfavorable mortality experience of women disappeared. When there were only few female policy holders, they were a bad sample, in regard to mortality, of females in general. An adage in the insurance business is that actual insurance applicants tend to be an unfavorable selection of all potential applicants. May this also be the case among overweight persons?

An independent approach to some of these problems is to study the relative obesity of cardiac patients. Studies on myocardial infarction all give the same answer. In Massachusetts,[7,8] in Tennessee,[2] in Minnesota,[12] and in the U. S. Army[15] the distribution of relative body weight among men when they suffer sudden myocardial infarction is substantially the same as among clinically healthy men of the same age, social class, and occupation.

The discussion so far has not differentiated between obesity and overweight. This is indefensible except on the practical grounds that in the literature on heart disease, previous discussions make no clear differentiation, and the concrete data which purport to refer to obesity actually turn out to be limited to relative body weight.

It is true that the extremes of overweight and underweight also correspond, more or less, to extremes of obesity and leanness or emaciation. But over the range represented by the great majority of the population, relative body weight is not a good measure of fatness.[3,14,4] The example of the overweight athlete who is remarkably lean is familiar. The sedentary businessman who is not overweight but still manages to be very fat is less obvious but more common and possibly more significant. Overweight from muscular development is

clearly in great metabolic contrast to overweight from excess fat, and the implications of the two conditions may be very different for the development of heart disease.

The appraisal of obesity from height-weight tables adjusted for "frame size" or "skeletal type" offers neither theoretical nor practical advantage.[14] On the practical side there is no system for classification of frame size, and on the theoretical side it is difficult to see how differentiation as to skeletal type can aid the distinction between fat and muscle. "Ideal weight" tables also fail to get at this problem.

At the present juncture, then, most of what has been suggested about the value of obesity control measures for the prevention of heart disease is on a very shaky foundation, to say the least. If the attack is to be directed against overweight, the most optimistic indications are that the result could not have any large effect on the heart disease mortality of the population. For the prevention of coronary disease the prospects are even poorer. Possibly more success could attend an attack on true obesity and excessive fatness, but the evidence is wanting and practical measures of fatness are not well developed. Skinfold calipers[3] offer considerable hope, but suitable calipers and standards for their use are not yet widely available. Until these are at hand the judgment of the examining physician, based on inspection and pinching, is perhaps the best criterion of fatness.

Clearly this is an important but neglected area of research. Methodological and normative studies on fatness are needed; and the results must be incorporated in a far more vigorous development of the epidemiology of heart disease. The recognition of the apparent limitations of the control of overweight for the prevention of heart disease points to the needs for investigation in this area. More intense study is needed for the role of dietary fat, of habitual physical activity, and of other factors which may be at the basis of the striking differences between populations in heart disease prevalence. In the meantime we may properly deplore obesity in general and should continue to urge weight reduction of cardiac patients. Optimism for *prevention* of heart disease through weight control is not justified at present, but this should mean only redoubling efforts to find other preventive measures of greater promise.

ANCEL KEYS

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MANAGEMENT OF POLYCYTHEMIA VERA

In the management of chronic disease two factors are often overlooked. One of these is concerned with the nature of the disorder, its natural course and prognosis, and the limitations as well as the potentialities of therapy. It is obvious that if the condition in question is comparatively benign and its course is slow the therapy which is undertaken must not be more dangerous than the disease. The second factor is related to the simplicity or complexity of the therapeutic measures chosen and their cost. If the course of the disease is prolonged, long-term success will naturally depend a good deal on the character of the measures chosen and on whether or not they tax the patient's financial resources.

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Polycythemia vera is a disease of insidious onset and chronic course, usually affecting those in the later years of life, and is characterized by an increase in the total blood volume and a variety of symptoms and signs such as a sense of fullness, headache, dizziness, ringing in the ears, visual disturbances, dyspnea, lassitude, or weakness. There may be such a multiplicity of symptoms that neurasthenia is suspected. A curious symptom is intense itching after a bath or when warm in bed. On the other hand, the symptoms may be insignificant, and the polycythemia may be discovered only accidentally.

The disorder is dangerous because of the complications which may ensue. Vascular disease is extremely common and vascular accidents are frequent and in many instances are the cause of death. Venous thromboses, varicosities, phlebitis, coronary thrombosis, claudication, arterial occlusion with gangrene, and hypertension are encountered in many cases. An unusually high proportion of patients develop peptic ulcer. Intercurrent infections, especially of the respiratory tract, chronic bronchitis, cirrhosis of the liver, and gout represent other less frequent complications. Although considerable attention has been given from time to time to various hypotheses concerning the nature of polycythemia vera, there has been little to change the view which is most generally held; namely, that this disorder represents a comparatively benign neoplastic condition which is related to chronic myelocytic leukemia and probably also to myelofibrosis. There is no doubt that, even prior to the use of radiation in the treatment of this disorder, a transition in some cases to chronic myelocytic leukemia or to acute myeloblastic leukemia took place.[1,5]

Both the symptoms of polycythemia vera and the frequency of its accompanying complications can be relieved by appropriate therapy. Reduction in blood volume can be achieved by one of three means: (1) removal of blood by venesection; (2) impairment of blood formation by the use of radiation or certain chemical agents, such as nitrogen mustard or related compounds; and (3) destruction of blood by the use of phenylhydrazine. In practice it is often found

that, in the course of the disease, all three methods need to be used at one time or another.

Venesection is the surest and safest means for reducing the blood volume. The amount removed depends on the original blood level. The goal is to bring the hemoglobin level and volume of packed red cells to normal or to approximately the upper limit of normal. The latter is suggested because sometimes these patients are found to be more comfortable at a level somewhat higher than the normal mean. The frequency of venesections will depend on the symptoms and the pleasure of the patient. One pint of blood may be removed every other day, or even daily in some patients. The theorectical objection to venesection, namely, that this stimulates erythropoiesis, is of little practical importance. The use of an iron-deficient diet to augment the iron deficiency produced by the venesections is impractical.

Venesection, however, often becomes a troublesome type of therapy if this procedure needs to be repeated at frequent intervals. For this reason it is the favored and recommended practice to reduce the blood volume to normal levels by venesection and to attempt to maintain it at such levels by other means. For this purpose radiation has many advantages.[1,4] As between roentgen therapy and radioactive phosphorus, the latter has the advantage that it is easily administered and there are no unpleasant aftereffects. The material can be given orally or intravenously but there is some value in intravenous administration in that there is no uncertainty regarding absorption. Although radioactive phosphorus has a widespread action at first because of the extensive participation of phosphorus in general biochemical processes, within one week appreciable amounts are deposited in bone and bone marrow and there the beta radiation affects the myeloid elements. A special advantage is derived from the fact that uptake of radioactive phosphorus by rapidly dividing cells is greater than by normal cells.

Generally a dose of 3 to 5 millicuries is recommended for the initial administration. The patient is seen at intervals of three to four weeks following this. If, after three or four months, it is apparent from the volume of packed red cells that the blood is not being maintained at near normal levels, another injection may be given, the amount depending on the blood level at the time. It is always wise to err on the side of giving too little rather than too much for, in the former case, blood can be removed if necessary, whereas if too much has been administered little can be done to correct the damage done.

From time to time some undesirable effect on the hemopoietic system is produced by administration of radioactive phosphorus, such as thrombocytopenia or granulocytopenia. Furthermore, radioactive phosphorus is not available in some communities. In such situations the administration of phenylhydrazine is to be recommended. This drug when given judiciously produces few or no ill effects and may be extremely valuable. The reports of thrombosis and severe hemolytic anemia associated with the administration of phenylhydrazine emanate from those who have used the drug for the initial reduction of blood volume to normal rather than for maintenance after preliminary venesection. The latter objective is achieved readily by giving 0.1 Gm. phenylhydrazine hydrochloride

in capsules, by mouth, two to six times a week. Until the required dose has been determined, the blood should be examined weekly. After a steady state has been achieved, these intervals may be prolonged but readjustment of the dose may be necessary from time to time.

In view of the effectiveness of the procedures described, there seems to be little justification for the use of agents of the toxicity of nitrogen mustard[3] or triethylene melamine.[2] By the judicious use of venesections, radioactive phosphorus, and phenylhydrazine the viscosity of the blood, as well as the total blood volume, can be reduced to satisfactory levels with a minimum of risk. The incidence of complications, especially vascular ones, has been greatly reduced in treated cases.[1,4] Whether or not the incidence of leukemia is somewhat higher in patients treated with radioactive phosphorus than in those not receiving this form of therapy is uncertain. In any event, the differences reported are not such as to dissuade one from the use of this valuable therapeutic agent.

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COMMENTS ON THE PATIENT WITH PROLONGED ILLNESS

Within the past decade considerable activity has taken place in the fields of medicine and public health in relation to the problem of chronic illness. National and local health and welfare bodies have met, conferred together, and contributed to the fund of general knowledge and to public awareness of many aspects of the problem, including the cost to the community in public and private monies and in social and economic productivity. Such concerted thought on the part of numerous professional individuals, with diverse special but related fields of interest, produces the groundwork for social legislation, for community organization, and for modification in established and traditional health services. One example of the latter is the accelerated movement in various parts of the country toward extension of hospital services into home care programs, hopefully for the greater benefit of patient and community alike.

Full recognition is here given to the need for all broad measures in the control of chronic disease. There is here no intent to diminish by one iota the value of such activities. In fact, their further expansion would be desirable. Indispensable and vital, they nevertheless constitute only *one* essential element in the effective solution of the basic problems.

Of at least equal importance is still another element—the direct service to the sick person as an individual. For plans and programs without sensitive translation into action on behalf of the ill patient himself become ineffectual, and fail in the real attainment of their goals. Professional workers in all health and welfare fields are today familiar with the broad concepts of the destructive force of chronic illness in the personal and family life of patients. Yet the questions arise: Why does the wide gap between theory and practice still prevail? How can the large body of existing knowledge be more effectively applied patient to patient? By what means can practitioners in all health and welfare fields be stimulated to put this knowledge into concrete daily use?

How can practitioners demonstrate realistically their understanding that the term "chronic" or "long-term" relates as much to the personal and social consequences to the patient, as to physical and emotional disease processes, and that their interrelationship, in fact, is the essence of the whole matter? With great and notable exceptions the sick person, with his unique constellation of circumstances, still remains less the focus of attention than his disease. In the pressures of private and clinic practice, inquiry into personal and environmental circumstances relevant to the patient's care is too often omitted, even when these may interfere with and reduce the maximum effectiveness of the medical treatment itself.

On the social side, the policy of many community welfare agencies to give high, if not exclusive, priority to service to people with interpersonal emotional

problems results in undervaluation of needs arising from physical illness, the neglect of which may indeed contribute to its chronicity and to the development of these social and interpersonal problems. Furthermore, while recognizing the existence of these special needs in all economic levels, leaders responsible for broad community social planning too infrequently move to provide new services or to include them in reorganized established agencies.

One might put the matter in a different way, and ask the question, how well is the individual sick person remembered? At the risk of oversimplification, a situation is here described which points up the basic problem under discussion—so self-evident as to be overlooked, but disturbing in consequences far beyond the intrinsic medical problem. A single woman living alone became homebound for several months with a crippling condition of a leg. Brief, unexplained medical orders—"keep off your feet"—were given without inquiry into or apparent concern for the possibility of the patient meeting even the most elementary physical needs. With explanation of neither the physical condition nor the consequences of ambulation, this emotionally independent patient struggled to manage alone. Even the absolute minimum of housekeeping necessary for self-respect involved use of the leg, prevented healing, aggravated the inflammation and pain, and markedly increased the incapacity. Since she was managing alone, shut indoors for many weeks, with difficulty in securing and preparing food, a poor nutritional state and general health deterioration resulted. Add to these primary difficulties the emotional problems of social isolation, insufficient diversional activities, anxiety about maintaining employment, loss of income plus the cost of medical supervision and drugs.

This situation, rudimentary and unspectacular, possibly even irritatingly simple, can be matched or even surpassed by all who read these comments. These are not the exclusive worries of people in low economic levels, but are realities alike for skilled and professional workers with incomes adequate in normal circumstances. Over and beyond the anxiety in many instances are the actual loss of employment and income, and inability to meet important obligations involving other persons. The cumulative personal distress and economic waste, moreover, are considerable and out of all proportion to the need for their existence.

Even in these days of more widespread appreciation of the bearing of social factors on health problems, too frequently the individual patient's personal and emotional needs remain obscured or forgotten in the greater and, at times, exclusive preoccupation with scientific matters and long-range public policy. The ultimate goals in these diverse aspects of chronic illness are identical. The question persists—by what means can their immediate realities be brought more closely into harmony?

To this perplexing question there appears to be no single answer. However, some roots of the problem reach far back into the nature of education of all the relevant professions, and into the habits of their practice. Recent advances in curriculum, although highly significant in aims, possibly may require greater scope and depth to bring about profound change in basic values. Be-

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sides, the vestigial remains of certain archaic institutional administrative policies and methods often defeat progressive changes in education, by failure to enable students to develop and maintain continuously that association of sound practice with theory which is indispensable to true learning. Further exploration in these areas should yield profitable results for the future.

ETHEL COHEN

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Book Reviews

THE HISTORY AND CONQUEST OF COMMON DISEASES. Edited by Walter R. Bett. Pp. 334; indexed. Norman, Oklahoma, 1954, University of Oklahoma Press. Price $4.00.

In this book there are taken up a series of the "common" diseases: influenza, tuberculosis, venereal disease, gallstones, appendicitis, epilepsy, cancer, malingering, and numerous others. What have this miscellany in common? Nothing except that they are frequently encountered. Each disease is discussed by a different author, but the same style is followed by all and a surprising degree of homogeneity results. On the whole these little historical sketches are good; they do however suffer from not being complete but are, rather, brief accounts with only partial bibliographies. However, the book should make pleasant and useful reading for the layman for whose benefit a glossary of medical terms is added. There is also an interesting list of proper names to which allusion is made in the text.

Arthur L. Bloomfield

ANNALS, Vol. 58, Art. 4, "THE COLON: ITS NORMAL AND ABNORMAL PHYSIOLOGY AND THERAPEUTICS." Monograph. By M. L. Tainter. Pp. 248; indexed. Illustrated. New York, 1954, The New York Academy of Sciences. Price $4.50.

As Dr. Almy says in his introductory remarks, this is a conference without precedent—a group of investigators assembled for the sole purpose of discussing the colon. Although cancer and specific infections are excluded from this discussion, an excellent attempt is made to probe the mysteries of this organ so obscure in its workings and so commonly deranged. On the panel we see such names as Tainter, Travell, Ingelfinger, Jordan, and Grimson, to mention only a few; on the program there are discussions of the physiology and pharmacology of the colon, etiology of colonic disorders, and management. Each section has some one-half dozen papers followed by a panel discussion. Some of the individual papers also have their own discussions, and in general those present try their best to get some order into the subject. The volume contains over 500 pages with tables, charts, and bibliographies.

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Books Received

HANDBOOK OF MEDICAL TREATMENT. Ed. 4. Edited by Milton J. Chatton, A.B., M.D., Sheldon Margen, M.A., M.D., and Henry D. Brainerd, A.B., M.D. Pp. 569; indexed. Los Altos, California, 1954, Lange Medical Publications. Price $3.00.

GENETICA MEDICA. By Luigi Gedda. Pp. 467; indexed. Rome, 1954, Edizioni Dell'Istituto Gregori Mendel.

ACTA GENETICAE MEDICAE ET GEMELLOLOGIAE. Vol. 3. Editor Luigi Gedda. Indirizzo della Redazione e dell'Amministrazione. Roma—Largo Dell'Amba Aradam, 1, 1954.

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